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1. Your reference 101211-1 GB

2. Patent application number *(The Patent Office will fill in this part)* 0321620.7

16SEP03 E837518-1 D02934
P01/7700 0.00-0321620.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation Sweden

7822448003

4. Title of the invention

QUINAZOLINE DERIVATIVES

5. Name of your agent *(if you have one)* Michael Andrew NELSON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
PO Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 8179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
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Continuation sheets of this form	
Description	80
Claim(s)	5
Abstract	
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 15.09.03

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer Bennett - 01625 230148

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QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for diseases resulting from the abnormal regulation of cellular proliferation such as psoriasis and cancer, utilise compounds that inhibit DNA synthesis and cellular proliferation. To date, compounds used in such treatments are generally toxic to cells however their enhanced effects on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to these cytotoxic anti-tumour agents are currently being developed, for example selective inhibitors of cell signalling pathways. These types of inhibitors are likely to have the potential to display an enhanced selectivity of action against tumour cells and so are likely to reduce the probability of the therapy possessing unwanted side effects.

Eukaryotic cells are continually responding to many diverse extracellular signals that enable communication between cells within an organism. These signals regulate a wide variety of physical responses in the cell including proliferation, differentiation, apoptosis and motility. The extracellular signals take the form of a diverse variety of soluble factors including growth factors as well as paracrine and endocrine factors. By binding to specific transmembrane receptors, these ligands integrate the extracellular signal to the intracellular signalling pathways, therefore transducing the signal across the plasma membrane and allowing the individual cell to respond to its extracellular signals. Many of these signal transduction processes utilise the reversible process of the phosphorylation of proteins that are involved in the promotion of these diverse cellular responses. The phosphorylation status of target proteins is regulated by specific kinases and phosphatases that are responsible for the regulation of about one third of all proteins encoded by the mammalian genome. As phosphorylation is such an important regulatory mechanism in the signal transduction process, it is therefore not surprising that aberrations in these intracellular pathways result in

abnormal cell growth and differentiation and so promote cellular transformation (reviewed in Cohen *et al*, Curr Opin Chem Biol, 1999, 3, 459-465).

It has been widely shown that a number of these tyrosine kinases are mutated to constitutively active forms and/or when over-expressed result in the transformation of a variety of human cells. These mutated and over-expressed forms of the kinase are present in a large proportion of human tumours (reviewed in Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248). As tyrosine kinases play fundamental roles in the proliferation and differentiation of a variety of tissues, much focus has centred on these enzymes in the development of novel anti-cancer therapies. This family of enzymes is divided into two groups - receptor and non-receptor tyrosine kinases e.g. EGF Receptors and the SRC family respectively. From the results of a large number of studies including the Human Genome Project, about 90 tyrosine kinase have been identified in the human genome, of this 58 are of the receptor type and 32 are of the non-receptor type. These can be compartmentalised in to 20 receptor tyrosine kinase and 10 non-receptor tyrosine kinase sub-families (Robinson *et al*, Oncogene, 2000, 19, 5548-5557).

The receptor tyrosine kinases are of particular importance in the transmission of mitogenic signals that initiate cellular replication. These large glycoproteins, which span the plasma membrane of the cell possess an extracellular binding domain for their specific ligands (such as Epidermal Growth Factor (EGF) for the EGF Receptor). Binding of ligand results in the activation of the receptor's kinase enzymatic activity that is encoded by the intracellular portion of the receptor. This activity phosphorylates key tyrosine amino acids in target proteins, resulting in the transduction of proliferative signals across the plasma membrane of the cell.

It is known that the erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells (reviewed in Olayioye et al., EMBO J., 2000, 19, 3159). One mechanism in which this can be accomplished is by overexpression of the receptor at the protein level, generally as a result of gene amplification. This has been observed in many common human cancers (reviewed in Klapper et al., Adv. Cancer Res., 2000, 77, 25) such as breast cancer (Sainsbury et al., Brit. J. Cancer, 1988, 58, 458; Guerin et al., Oncogene Res., 1988, 3, 21; Slamon et al., Science, 1989, 244, 707; Klijn et al., Breast Cancer Res. Treat., 1994, 29, 73 and reviewed in Salomon et al., Crit. Rev. Oncol. Hematol., 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny et al., Brit. J. Cancer, 1986, 54,

265; Reubi et al., Int. J. Cancer, 1990, 45, 269; Rusch et al., Cancer Research, 1993, 53, 2379; Brabender et al, Clin. Cancer Res., 2001, 7, 1850) as well as other cancers of the lung (Hendler et al., Cancer Cells, 1989, 7, 347; Ohsaki et al., Oncol. Rep., 2000, 7, 603), bladder cancer (Neal et al., Lancet, 1985, 366; Chow et al., Clin. Cancer Res., 2001, 7, 1957, Zhau et al., Mol Carcinog., 3, 254), oesophageal cancer (Mukaida et al., Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen et al., Oncogene Res., 1987, 1, 149; Kapitanovic et al., Gastroenterology, 2000, 112, 1103; Ross et al., Cancer Invest., 2001, 19, 554), cancer of the prostate (Visakorpi et al., Histochem. J., 1992, 24, 481; Kumar et al., 2000, 32, 73; Scher et al., J. Natl. Cancer Inst., 2000, 92, 1866), leukaemia (Konaka et al., Cell, 1984, 37, 1035, Martin-Subero et al., Cancer Genet Cytogenet., 2001, 127, 174), ovarian (Hellstrom et al., Cancer Res., 2001, 61, 2420), head and neck (Shiga *et al.*, Head Neck, 2000, 22, 599) or pancreatic cancer (Ovotny et al., Neoplasma, 2001, 48, 188). As more human tumour tissues are tested for expression of the erbB family of receptor tyrosine kinases it is expected that their widespread prevalence and importance will be further enhanced in the future.

As a consequence of the mis-regulation of one or more of these receptors, it is widely believed that many tumours become clinically more aggressive and so correlate with a poorer prognosis for the patient (Brabender et al, Clin. Cancer Res., 2001, 7, 1850; Ross et al, Cancer Investigation, 2001, 19, 554, Yu et al., Bioessays, 2000, 22.7, 673). In addition to these clinical findings, a wealth of pre-clinical information suggests that the erbB family of receptor tyrosine kinases are involved in cellular transformation. This includes the observations that many tumour cell lines overexpress one or more of the erbB receptors and that EGFR or erbB2 when transfected into non-tumour cells have the ability to transform these cells. This tumourigenic potential has been further verified as transgenic mice that overexpress erbB2 spontaneously develop tumours in the mammary gland. In addition to this, a number of pre-clinical studies have demonstrated that anti-proliferative effects can be induced by knocking out one or more erbB activities by small molecule inhibitors, dominant negatives or inhibitory antibodies (reviewed in Mendelsohn et al., Oncogene, 2000, 19, 6550). Thus it has been recognised that inhibitors of these receptor tyrosine kinases should be of value as a selective inhibitor of the proliferation of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933, Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248; Al-Obeidi *et al*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al*, 2000, Oncogene, 19, 6550-6565).

Recently the small molecule EGFR tyrosine kinase inhibitor, Iressa (also known as gefitinib, and ZD1834) has been approved for use in the treatment of advanced non-small cell lung cancer. Furthermore, findings using inhibitory antibodies against EGFR and erbB2 (c-225 and trastuzumab respectively) have proven to be beneficial in the clinic for the treatment of selected solid tumours (reviewed in Mendelsohn *et al*, 2000, Oncogene, 19, 6550-6565).

Amplification and/or activity of members of the erbB receptor tyrosine kinases have been detected and so have been implicated to play a role in a number of non-malignant proliferative disorders such as psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, 6, 933; Elder et al., Science, 1989, 243, 811), benign prostatic hyperplasia (BPH) (Kumar et al., Int. Urol. Nephrol., 2000, 32,73), atherosclerosis and restenosis (Bokemeyer et al., Kidney Int., 2000, 58, 549). It is therefore expected that inhibitors of erbB receptor tyrosine kinases will be useful in the treatment of these and other non-malignant disorders of excessive cellular proliferation.

European patent application EP 566 226 discloses certain 4-anilinoquinazolines that are receptor tyrosine kinase inhibitors.

International patent applications WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980, WO 96/33981, WO 97/30034, WO 97/38994 disclose that certain quinazoline derivatives which bear an anilino substituent at the 4-position and a substituent at the 6- and/or 7- position possess receptor tyrosine kinase inhibitory activity.

European patent application EP 837 063 discloses aryl substituted 4-aminoquinazoline derivatives carrying moiety containing an aryl or heteroaryl group at the 6-or 7- position on the quinazoline ring. The compounds are stated to be useful for treating hyperproliferative disorders.

International patent applications WO 97/30035 and WO 98/13354 disclose certain 4-anilinoquinazolines substituted at the 7- position are vascular endothelial growth factor receptor tyrosine kinase inhibitors.

WO 00/55141 discloses 6,7-substituted 4-anilinoquinazoline compounds characterised in that the substituents at the 6-and/or 7-position carry certain ester groups.

WO 00/56720 discloses 6,7-dialkoxy-4-anilinoquinazoline compounds for the treatment of cancer or allergic reactions.

WO01/21596 discloses the use of certain 4-anilinoquinazoline derivatives as aurora 2 kinase inhibitors.

WO 02/18351 and WO 02/18372 disclose certain 4-anilinoquinazoline compounds substituted at the 6- and/or 7- position which are stated to have an inhibitory effect upon signal transduction mediated by tyrosine kinases.

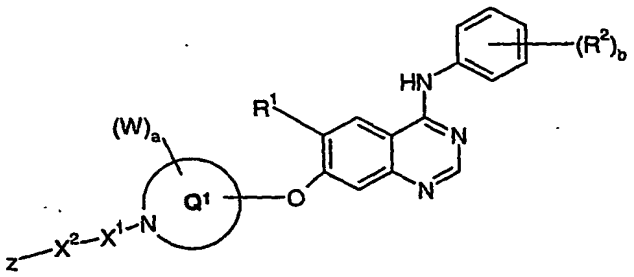
WO 02/41882 discloses 4-anilinoquinazoline compounds substituted at the 6- and/or 7- position by a substituted pyrrolidinyl-alkoxy or piperidinyl-alkoxy group.

We have now found that surprisingly certain quinazoline derivatives substituted at the 7-position with a substituent containing certain substituted alkanoyl groups possess potent anti-tumour activity. The compounds of the present invention also possess improved cellular potency, and favourable physical properties, particularly solubility, which may provide advantages in the formulation and delivery of the compound to patients.

Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the erbB family of receptor tyrosine kinases that are involved in the signal transduction steps which lead to the proliferation of tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of EGFR receptor tyrosine kinase.

Generally the compounds of the present invention possess potent inhibitory activity against the erbB receptor tyrosine kinase family, for example by inhibition of EGFR and/or erbB2 and/or erbB4 receptor tyrosine kinases, whilst possessing less potent inhibitory activity against other kinases. Furthermore, the compounds of the present invention possess substantially better potency against the EGFR tyrosine kinase over that of the erbB2 tyrosine kinase. Accordingly, it may be possible to administer a compound according to the present invention at a dose that is sufficient to inhibit EGFR tyrosine kinase whilst having no significant effect upon erbB2 (or other) tyrosine kinases. The selective inhibition provided by the compounds according to the present invention may provide treatments for conditions mediated by EGFR tyrosine kinase, whilst reducing undesirable side effects that may be associated with the inhibition of other tyrosine kinases.

According to a first aspect of the invention there is provided a quinazoline derivative of the Formula I:



I

wherein:

R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is a direct bond or is O, and Q^2 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^3)$, CO, $CH(OR^3)$, $CON(R^3)$, $N(R^3)CO$, $SO_2N(R^3)$, $N(R^3)SO_2$, CH=CH and C≡C wherein R^3 is hydrogen or (1-6C)alkyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^3-X^4-$$

wherein X^3 is a direct bond or is selected from CO and $N(R^4)CO$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,

N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:

$$-X^5-Q^4$$

wherein X^4 is a direct bond or is selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, $C(R^5)_2O$, $C(R^5)_2S$ and $C(R^5)_2N(R^5)$, wherein R^5 is hydrogen or (1-6C)alkyl, and Q^4 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears one or more (for example 1, 2 or 3) substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, mercapto, sulfamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:

$$-X^6-R^6$$

wherein X^6 is a direct bond or is selected from O, $N(R^7)$ and C(O), wherein R^7 is hydrogen or (1-6C)alkyl, and R^6 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

b is 1, 2, 3, 4 or 5;

each R^2, which may be the same or different, is selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-
(1-6C)alkanesulphonylamino and a group of the formula :

$$-X^7-R^8$$

wherein X^7 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl;

Q^1 is piperidinyl;

a is 0, 1, 2, 3 or 4;

each W, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, oxo, amino, formyl, mercapto, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^8-R^{10}$$

wherein X^8 is a direct bond or is selected from O, CO, SO_2 and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and R^{10} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, N-(1-6C)alkylamino-(1-6C)alkyl or N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl;

X^1 is selected from CO and SO_2;

X^2 is a group of the formula:

$$-(CR^{12}R^{13})_p-(Q^5)_m-(CR^{14}R^{15})_q-$$

wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

each of R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, is selected from hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q^5 is selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,

and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:

$$Q^6\text{-}X^9\text{-}$$

wherein X^9 is a direct bond or is selected from O, $N(R^{16})$, SO_2 and $SO_2N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl;

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^{17})$, CO, -C=C- and -C≡C- wherein R^{17} is hydrogen or (1-6C)alkyl,

and wherein and wherein any CH_2 or CH_3 group within any Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^{10}\text{-}R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

provided that:

when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino and R^1 is hydrogen or (1-3C)alkoxy, then a is 0 and Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q^6-X^9-;

or a pharmaceutically acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. It is further to be understood that in the names of chiral compounds (*R*,*S*) denotes any scalemic or racemic mixture while (*R*) and (*S*) denote the enantiomers. In the absence of (*R*,*S*), (*R*) or (*S*) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains *R* and *S* enantiomers in any relative proportions and a racemic mixture contains *R* and *S* enantiomers in the ratio 50:50. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the

above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (for example Q^2, Q^4 or Q^6) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' or R group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (for example Q^2, Q^4 or Q^6) when it is (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl. It is to be understood that reference to (3-7C)cycloalkylene used herein for Q^5 refers to a divalent (3-7C)cycloalkane linking group, which group may be linked via different carbon atoms in the (3-7C)cycloalkylene ring, or which may be linked via a single carbon atom in the (3-7C)cycloalkylene ring. Accordingly, reference to, for example, a "cyclopropylene" group includes cycloprop-1,2-ylene and a cyclopropylidene group of the formula:

However references to an individual (3-7C)cycloalklene group such as cyclopropylidene are specific for that group only. A silmilar convention is adopted for the (3-7C)cycloalkenylene groups represented by Q^5.

A suitable value for any one of the 'Q' groups (for example Q^2, Q^3, Q^4 or Q^6) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated (i.e. ring systems with the maximum degree of saturation) or partially saturated (i.e. ring systems retaining some, but not the full, degree of unsaturation) 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, which, unless specified otherwise, may be carbon or nitrogen linked, for example oxiranyl, oxetanyl, azetidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, decahydroisoquinolinyl or decahydroquinolinyl, particularly tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,4-oxazepanyl, thiamorpholinyl 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl, more particularly tetrahydrofuran-3-yl, tetrahydropyran-4-yl,

tetrahydrothien -3-yl, tetrahydrothiopyran-4-yl, pyrrolidin-1-yl pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, morpholin-2-yl, piperidino, piperidin-4-yl, piperidin-3-yl, piperidin-2-yl or piperazin-1-yl. A nitrogen or sulphur atom within a heterocyclyl group may be oxidized to give the corresponding N or S oxide, for example 1,1-dioxotetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothiopyranyl or 1-oxotetrahydrothiopyranyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heterocyclyl-(1-6C)alkyl is, for example, heterocyclylmethyl, 2-heterocyclylethyl and 3-heterocyclylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heterocyclyl-(1-6C)alkyl group, an (3-7C)cycloalkyl-(1-6C)alkyl or (3-7C)cycloalkenyl-(1-6C)alkyl is present.

Suitable values for any of the 'R' groups (R^1 to R^{19}), W, or for various groups within a X^1, X^2 or Z group include:-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl and ethylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl and ethylsulphonyl;
for (1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

for N,N-di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (2-6C)alkanoyl:	acetyl, propionyl, butyryl and isobuyryl;
for (2-6C)alkanoyloxy:	acetoxy and propionyloxy;
for (2-6C)alkanoylamino:	acetamido and propionamido;
for N-(1-6C)alkyl-(2-6C)alkanoylamino:	N-methylacetamido and N-methylpropionamido;
for N-(1-6C)alkylsulphamoyl:	N-methylsulphamoyl and N-ethylsulphamoyl;
for N,N-di-[(1-6C)alkyl]sulphamoyl:	N,N-dimethylsulphamoyl;
for (1-6C)alkanesulphonylamino:	methanesulphonylamino and ethanesulphonylamino;
for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino:	N-methylmethanesulphonylamino and N-methylethanesulphonylamino;
for (3-6C)alkenoylamino:	acrylamido, methacrylamido and crotonamido;
for N-(1-6C)alkyl-(3-6C)alkenoylamino:	N-methylacrylamido and N-methylcrotonamido;
for (3-6C)alkynoylamino:	propiolamido;
for N-(1-6C)alkyl-(3-6C)alkynoylamino:	N-methylpropiolamido;
for amino-(1-6C)alkyl:	aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
for (1-6C)alkylamino-(1-6C)alkyl:	methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
for di-[(1-6C)alkyl]amino-(1-6C)alkyl:	dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
for halogeno-(1-6C)alkyl:	chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;
for hydroxy-(1-6C)alkyl:	hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
for (1-6C)alkoxy-(1-6C)alkyl:	methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
for cyano-(1-6C)alkyl:	cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;

for (1-6C)alkylthio-(1-6C)alkyl: methylthiomethyl, ethylthiomethyl, 2-methylthioethyl, 1-methylthioethyl and 3-methylthiopropyl;

for (1-6C)alkylsulphinyl-(1-6C)alkyl: methylsulphinylmethyl, ethylsulphinylmethyl, 2-methylsulphinylethyl, 1-methylsulphinylethyl and 3-methylsulphinylpropyl;

for (1-6C)alkylsulphonyl-(1-6C)alkyl: methylsulphonylmethyl, ethylsulphonylmethyl, 2-methylsulphonylethyl, 1-methylsulphonylethyl and 3-methylsulphonylpropyl;

for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl;

for N-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl: N-methylacetamidomethyl, 2-(N-methylacetamido)ethyl and 2-(N-methylpropionamido)ethyl;

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminoethyl;

(2-6C)alkanoyloxy-(1-6C)alkyl: acetoxymethyl, 2-acetoxyethyl and 2-propionyloxyethyl;

for carbamoyl-(1-6C)alkyl: carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl;

for (2-6C)alkanoyl-(1-6C)alkyl: acetylmethyl and 2-acetylethyl;

for N-(1-6C)alkylcarbamoyl-(1-6C)alkyl: N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, N-propylcarbamoylmethyl, 1-(N-methylcarbamoyl)ethyl, 1-(N-ethylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N-ethylcarbamoyl)ethyl and 3-(N-methylcarbamoyl)propyl;

for N,N-di[(1-6C)alkyl]carbamoyl-(1-6C)alkyl: N,N-dimethylcarbamoylmethyl, N,N-diethylcarbamoylmethyl, 2-(N,N-dimethylcarbamoyl)ethyl, and 3-(N,N-dimethylcarbamoyl)propyl;

for sulfamoyl(1-6C)alkyl: sulfamoylmethyl, 1-sulfamoylethyl, 2-sulfamoylethyl and 3-sulfamoylpropyl;

for N-(1-6C)alkylsulfamoyl(1-6C)alkyl: N-methylsulfamoylmethyl, N-ethylsulfamoylmethyl, N-propylsulfamoylmethyl, 1-(N-methylsulfamoyl)ethyl, 2-(N-methylsulfamoyl)ethyl and 3-(N-methylsulfamoyl)propyl; and

for N,N di-(1-6C)alkylsulfamoyl(1-6C)alkyl: N,N-dimethylsulfamoylmethyl, N,N-diethylsulfamoylmethyl, N methyl,N-ethylsulfamoylmethyl, 1-(N,N-dimethylsulfamoyl)ethyl, 1-(N,N-diethylsulfamoyl)ethyl, 2-(N,N-dimethylsulfamoyl)ethyl, 2-(N,N-diethylsulfamoyl)ethyl and 3-(N,N-dimethylsulfamoyl)propyl.

When, as defined hereinbefore Z in Formula I is a group of the formula Q^6-X^9-, and X^9 is $SO_2N(R^{16})$, the SO_2 group is attached to Q^6 and the nitrogen atom is attached to X^2 in Formula I. The same convention is applied to other groups defined herein. For example when X^2 is a group of the formula Q^5-$(CR^{14}R^{15})_m$, the Q^5 group is attached to the group Z in Formula I and the $(CR^{14}R^{15})_m$ group is attached to the X^1 group in Formula I.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within, for example, a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^3)$, $N(R^3)$ or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group. It is to be understood that the term (2-6C)alkylene chain refers to any CH_2CH_2 group within R^1 and includes, for example alkylene chains within a (1-6C)alkyl, (1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkenyloxy, (2-8C)alkynyl and (2-8C)alkynyloxy group. For example the

insertion of a $N(CH_3)$ group between the third and fourth carbon atoms in a hex-5-enyloxy group in R^1 gives rise to a 3-(N-methyl-N-allylamino)propoxy group.

When, as defined hereinbefore, any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent such as a group of the formula Q^3-X^4- wherein X^4 is, for example, NHCO and Q^3 is a heterocyclyl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When reference is made herein to a CH_2 or CH_3 group optionally bearing on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

Where reference is made herein to any CH_2 or CH_3 group optionally bearing on each said CH_2 or CH_3 group a substituent as defined herein, suitable substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, and hydroxy-substituted (2-6)alkanoyl groups such as hydroxyacetyl, 2-hydroxypropionyl and 2-hydroxybutyryl.

For the avoidance of doubt, when W is oxo, a CH_2 in Q^1 is substituted by O to give a C(O) group.

It is to be understood that reference herein to Q^1 being, for example piperidin-4-yl refers to the attachment of the piperidine ring to the oxygen in Formula I. The piperidine ring is further substituted at the 1-position by the group $Z-X^2-X^1-$ and optionally bears one or more W substituents on one or more of the available ring carbon atoms.

It is to be understood that certain compounds of the Formula I may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase.

It is also to be understood that certain compounds of the Formula I may exhibit polymorphism, and that the invention encompasses all such forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase.

It is also to be understood that the invention relates to all tautomeric forms of the compounds of the Formula I forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of R^1, R^2, W, Q^1, X^1, X^2, a, b and Z has any of the meanings defined hereinbefore or in paragraphs (a) to (ttt) hereinafter:-

(a) R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is a direct bond or is O, and Q^2 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^3)$, $CON(R^3)$, $N(R^3)CO$, CH=CH and C≡C wherein R^3 is hydrogen or (1-6C)alkyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^3-X^4-$$

wherein X^4 is a direct bond or is selected from CO and $N(R^4)CO$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano, carbamoyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$ and $C(R^5)_2O$, wherein R^5 is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, or from a group of the formula:

$$-X^6-R^6$$

wherein X^6 is a direct bond or is selected from O and $N(R^7)$, wherein R^7 is hydrogen or (1-6C)alkyl, and R^6 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl and N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(b) R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is a direct bond or is O, and Q^2 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^3)$, $CON(R^3)$, $N(R^3)CO$, CH=CH and C≡C wherein R^3 is hydrogen or (1-6C)alkyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl,

N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl

and wherein any CH_2 or CH_3 group within a R^1 substituent, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano, carbamoyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or from a group of the formula :

$$-X^5-Q^5$$

wherein X^5 is a direct bond or is selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$ and $C(R^5)_2O$, wherein R^5 is hydrogen or (1-6C)alkyl, and Q^5 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, or from a group of the formula:

$$-X^6-R^6$$

wherein X^6 is a direct bond or is selected from O and $N(R^7)$, wherein R^7 is hydrogen or (1-6C)alkyl, and R^6 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(c) R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^3)$, $CON(R^3)$, $N(R^3)CO$, CH=CH and C≡C wherein R^3 is hydrogen or (1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano, carbamoyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl;

(d) R^1 is selected from hydrogen, hydroxy, methoxy, ethoxy, propoxy, isopropyloxy, 2-hydroxyethoxy, 2-fluoroethoxy, cyclopropylmethoxy, 2-cyclopropylethoxy, vinyloxy, allyloxy, ethynyloxy, 2-propynyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofurfuryloxy, tetrahydrofuran-3-ylmethoxy, 2-(tetrahydrofuran-2-yl)ethoxy, 3-(tetrahydrofuran-2-yl)propoxy, 2-(tetrahydrofuran-3-yl)ethoxy, 3-(tetrahydrofuran-3-yl)propoxy, tetrahydropyranylmethoxy, 2-tetrahydropyranylethoxy, 3-tetrahydropyranylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino and piperazin-1-yl;

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, $N(CH_3)$,CH=CH and C≡C,

and when R^1 is a vinyloxy, allyloxy, ethynyloxy or 2-propynyloxy group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :

$$Q^3\text{-}X^4\text{-}$$

wherein X^4 is a direct bond or is NHCO or $N(CH_3)CO$ and Q^3 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 group which is attached to 2 carbon atoms (other than a CH_2 group within a heterocyclyl ring) or any CH_3 group which is attached to a carbon atom within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, ethoxy, methylsulfonyl, methylamino and dimethylamino,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methyl, ethyl, n-propyl, isopropyl and methoxy, and any piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, or piperazin-1-yl group within a R^1 substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetyl or propionyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(e) R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (3-7C)cycloalkyl-oxy and (3-7C)cycloalkyl-(1-6C)alkoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, oxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, N-(1-6C)alkylsulfamoyl and N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino;

(f) R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (3-7C)cycloalkyl-oxy and (3-7C)cycloalkyl-(1-6C)alkoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro substituents, or a substituent selected from hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

(g) R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (3-7C)cycloalkyl-oxy and (3-7C)cycloalkyl-(1-6C)alkoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of an O atom,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro substituents, or a substituent selected from hydroxy and (1-4C)alkoxy;

(h) R^1 is selected from hydrogen, (1-6C)alkoxy, cyclopropyl-(1-4C)alkoxy, cyclobutyl-(1-4C)alkoxy, cyclopentyl-(1-4C)alkoxy, cyclohexyl-(1-6C)alkoxy, tetrahydrofuranyl-(1-4C)alkoxy and tetrahydropyranyl-(1-4C)alkoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of an O atom,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro substituents, or a substituent selected from hydroxy and (1-3C)alkoxy;

(i) R^1 is selected from hydrogen, (1-6C)alkoxy, cyclopropylmethoxy and 2-cyclopropylethoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro substituents, or a substituent selected from hydroxy, methoxy and ethoxy;

(j) R^1 is selected from hydrogen methoxy, ethoxy, propyloxy, isopropyloxy, cyclopropylmethoxy, 2-hydroxyethoxy, 2-fluoroethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy;

(k) R^1 is selected from hydrogen and (1-3C)alkoxy;

(l) R^1 is hydrogen;

(m) R^1 is methoxy;

(n) each R^2, which may be the same or different, is selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy, and a group of the formula :

$$-X^7-R^8$$

wherein X^7 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl;

(o) each R^2, which may be the same or different, is selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(p) each R^2, which may be the same or different, is selected from fluoro, chloro, bromo, iodo, cyano, hydroxy, trifluoromethyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl and (1-4C)alkoxy;

(q) each R^2, which may be the same or different, is selected from fluoro, chloro, bromo, iodo, cyano, carbamoyl, hydroxy, trifluoromethyl, methyl, ethyl, isopropyl, methoxy, ethoxy, vinyl, allyl, ethynyl, 1-propynyl, 2-propynyl, N-methylcarbamoyl, N-ethylcarbamoyl and N,N-dimethylcarbamoyl;

(r) each R^2, which may be the same or different, is selected from fluoro, chloro, bromo, iodo, cyano, hydroxy, trifluoromethyl, methyl, ethyl, isopropyl, methoxy, ethoxy, vinyl, allyl, ethynyl, 1-propynyl, and 2-propynyl;

(s) each R^2, which may be the same or different, is selected from fluoro, chloro, bromo, cyano, hydroxy, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and ethynyl;

(t) each R^2, which may be the same or different, is selected from halogeno (particularly fluoro, chloro and bromo);

(u) b is 1, 2 or 3 and one R^2 is at the meta (3-) position on the anilino group;

(v) b is 1, 2 or 3 and each R^2, which may be the same or different, is as defined in any of (n) to (t) above;

(w) b is 1, 2 or 3, one R^2 is at the meta (3-) position on the anilino group and is halogeno, and when b is 2 or 3 the other R^2 group(s), which may be the same or different, are as defined in any of any of (n) to (t) above;

(x) b is 1, 2 or 3, each R^2, which may be the same or different, is halogeno, and wherein one R^2 is at the meta (3-) position on the anilino group;

(y) b is 1 or 2, each R^2, which may be the same or different, is halogeno (particularly fluoro, chloro or bromo) and wherein one R^2 is at the meta (3-) position and the other R^2 is at the ortho (2-) or para (4-) position on the anilino group;

(z) b is 1 or 2, one R^2 is at the meta (3-) position on the anilino group and is chloro, and when b is 2 or 3 the other R^2 group(s), which may be the same or different, are selected from fluoro, chloro and bromo;

(aa) the anilino group at the 4-position in the compound of Formula I is selected from 3-chloro-4-fluoroanilino, 3-chloro-2-fluoroanilino, 2-fluoro-5-chloroanilino, 3-bromoanilino, 3-methylanilino and 3-ethynylanilino;

(bb) the anilino group at the 4-position in the compound of Formula I is 3-chloro-4-fluoroanilino;

(cc) the anilino group at the 4-position in the compound of Formula I is 3-chloro-2-fluoroanilino;

(dd) Q^1 is selected from piperidin-3-yl and piperidin-4-yl;

(ee) Q^1 is piperidin-4-yl;

(ff) each W, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, oxo, (1-6C)alkyl, (1-6C)alkoxy, and from a group of the formula:

$$-X^8-R^{10}$$

wherein X^8 is a direct bond or is O, and R^{10} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;

(gg) each W, which may be the same or different, is selected from halogeno, hydroxy, oxo, (1-6C)alkyl and (1-6C)alkoxy;

(hh) each W, which may be the same or different, is selected from halogeno (particularly fluoro), hydroxy, (1-3C)alkyl and (1-3C)alkoxy;

(ii) a is 0, 1, or 2 and each W, which may be the same or different, is as defined in any of (ff) to (hh);

(jj) a is 0 or 1 and W is as defined in any of (ff) to (hh);

(kk) a is 0;

(ll) Q^1 is piperidin-4-yl, a is 0 or 1 and W is as defined in any of (ff) to (hh);

(mm) X^1 is CO;

(nn) X^1 is SO_2;

(oo) X^2 is a group of the formula:

$$-(CR^{12}R^{13})_p-(Q^5)_m-(CR^{14}R^{15})_q-$$

wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

each of R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, is selected from hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q^5 is selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,

and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(pp) X^2 is selected from a group of the formula $-(Q^5)_m-(CR^{14}R^{15})_q-$ and a group of the formula $-(CR^{12}R^{13})_q-(Q^5)_m-$, wherein m is 0 or 1, q is 1, 2, 3 or 4, and Q^5, R^{12}, R^{13}, R^{14} and R^{15} are as hereinbefore defined;

(qq) X^2 is a group of the formula $-Q^5-$, for example (3-7C)cycloalkylene such as cyclopropylidene;

(rr) X^2 is selected from cyclopropylene, cyclopbutylene, cyclopentylene, cyclohexylene, methylene-(3-6C)cycloalkylene, (3-6C)cycloalkylene-methylene-, ethylene-(3-6C)cycloalkylene and (3-6C)cycloalkylene-ethylene-,

and wherein and wherein any CH_2 or CH_3 group within X^2, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(ss) X^2 is a group of the formula $-(CR^{12}R^{13})_q-$,

q is 1, 2, 3 or 4,

each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

and wherein and wherein any CH_2 or CH_3 group within X^2, optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(tt) X^2 is a group of the formula $-(CR^{12}R^{13})_q-$,

q is 1, 2 or 3,

each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, and (1-6C)alkoxy,

(uu) X^2 is a group of the formula $-(CR^{12}R^{13})_q-(CR^{12a}R^{13a})-$,

q is 1, 2 or 3,

each of R^{12}, R^{13} and R^{13a}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

R^{12a} is selected from amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(vv) X^{12} is a group of the formula $-(CR^{12}R^{13})_q-$,

q is 1, 2, 3 or 4,

each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl, provided that at least one of R^{12} or R^{13} is (1-6C)alkyl,

and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, and (1-6C)alkoxy;

(ww) X^2 is selected from a group of the formula $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$, $-(CR^{12}R^{13}CH_2CH_2)-$, $-(CH_2CR^{12}R^{13})-$ and $-(CH_2CH_2CR^{12}R^{13})-$,

each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

and wherein any CH_2 or CH_3 group within X^2, optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2

or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(xx) X^2 is selected from a group of the formula $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$, $-(CR^{12}R^{13}CH_2CH_2)-$, $-(CH_2CR^{12}R^{13})-$ and $-(CH_2CH_2CR^{12}R^{13})-$,

each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl, provided that at least one of R^{12} or R^{13} is a branched (1-6C)alkyl group,

and wherein any CH_2 or CH_3 group within X^2, optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(yy) X^2 is selected from a group of the formula $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$, $-(CR^{12}R^{13}CH_2CH_2)-$, $-(CH_2CR^{12}R^{13})-$ and $-(CH_2CH_2CR^{12}R^{13})-$,

each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl, provided that at least one of R^{12} or R^{13} in X^2 is a branched alkyl group selected from iso-propyl, iso-butyl, sec-butyl and tert-butyl,

and wherein any CH_2 or CH_3 group within X^2, optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro substituents,

and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy and (1-3C)alkoxy;

(zz) X^2 is selected from a group of the formula $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$ and $-(CH_2CR^{12}R^{13})-$

wherein each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl and (1-4C)alkoxy-(1-4C)alkyl, provided that R^{12} and R^{13} are not both hydrogen;

(aaa) X^2 is selected from a group of the formula $-CH_2-$, $-CH_2CH_2-$, $-(CHR^{12a})-$, $-(CHR^{12a}CH_2)-$ and $-(CH_2CHR^{12b})-$

wherein R^{12a} is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl,

and wherein R^{12b} is selected from hydrogen, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl;

(bbb) X^2 is selected from a group of the formula $-CH_2-$, $-CH_2CH_2-$, $-(CHR^{12})-$, $-(CHR^{12}CH_2)-$ and $-(CH_2CHR^{12})-$

wherein R^{12} is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl;

(ccc) X^2 is selected from a group of the formula $-(CH_2)_q-$, wherein q is 1, 2 or 3, particularly q is 1 or 2;

(ddd) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:

$$Q^6\text{-}X^9\text{-}$$

wherein X^9 is a direct bond or is selected from O, $N(R^{16})$, SO_2 and $SO_2N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein any heterocyclyl group in Z is a monocyclic a fully saturated 4, 5, 6 or 7-membered monocyclic heterocyclyl group containing 1 or 2 heteroatoms selected from oxygen, nitrogen and sulfur,

and wherein and wherein any CH_2 or CH_3 group within a Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^{10}-R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

(eee) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy and a group of the formula:

$$Q^6-X^9-$$

wherein X^9 is a direct bond or is selected from O and $N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein any heterocyclyl group in Z is a monocyclic a non-aromatic fully saturated or partially saturated 4, 5, 6 or 7-membered monocyclic heterocyclyl group containing 1 heteroatom selected from oxygen and nitrogen and optionally a further heteroatom selected from oxygen, nitrogen and sulfur,

and wherein and wherein any CH_2 or CH_3 group within a Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^{10}-R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

(fff) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy and a group of the formula:

$$Q^6-X^9-$$

wherein X^9 is a direct bond or is selected from O and $N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein any heterocyclyl group in Z is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl group may be carbon or nitrogen linked to the group to which it is attached,

and wherein and wherein any CH_2 or CH_3 group within a Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^{10}-R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

(ggg) Z is selected from hydroxy, amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-(1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl homopiperazin-1-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl and a group of the formula:

$$Q^6\text{-}X^9\text{-}$$

wherein X^9 is selected from O and $N(R^{16})$, wherein R^{16} is hydrogen or (1-4C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein any heterocyclyl group in Q^6 is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, which heterocyclyl group may be carbon or nitrogen linked to the group to which it is attached,

and wherein and wherein any CH_2 or CH_3 group within a Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^{10}-R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

(hhh) Z is selected from amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-(1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl and homopiperazin-1-yl,

and wherein and wherein any CH_2 or CH_3 group within a Z group, optionally bears on each said CH_2 or CH_3 group one or more fluoro substituents or a substituent selected from hydroxy, cyano, amino, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, cyano, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkanoyl, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

(iii) Z is selected from hydroxy, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl and a group of the formula:

$$Q^{6}-X^{9}-$$

wherein X^9 is O, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein any heterocyclyl group in Z is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl and oxepanyl,

and wherein any CH_2 or CH_3 group within a Z group, optionally bears on each said CH_2 or CH_3 group one or more fluoro substituents or a substituent selected from hydroxy, cyano, amino, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, cyano, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

(jjj) Z is selected from hydroxy, amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-(1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy and (1-4C)alkoxy-(2-6C)alkoxy;

(kkk) Z is selected from hydroxy, methoxy, ethoxy, 2-hydroxyethoxy, 2-methoxyethoxy, amino, methylamino, ethylamino, N-(2-hydroxyethyl)amino, N-(2-methoxyethyl)amino, dimethylamino, N-methyl-N-ethylamino, di-ethylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxyethyl)-N-ethylamino, N,N-di-(2-hydroxyethyl)amino, N-(2-methoxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-ethylamino, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, tetrahydrofuranyl and tetrahydropyranyl,

and wherein any heterocyclyl group within Z optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (2-4C)alkanoyl and (1-4C)alkoxy;

(lll) Z is selected from pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl, homopiperazin-1-yl, (particularly Z is selected from pyrrolidin-1-yl, piperidino, piperazin-1-yl and morpholino),

and wherein the heterocyclyl group within Z optionally bears one or more (for example 1, 2 or 3) substituents, which may be the same or different selected from fluoro, chloro, cyano, hydroxy, amino, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, acetyl, propionyl, 2-fluoroethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl, hydroxyacetyl, aminoacetyl, methylaminoacetyl, ethylaminoacetyl, dimethylaminoacetyl and N-methyl-N-ethylaminoacetyl;

(mmm) Z is hydroxy;

(nnn) Z is as defined in any of (ddd) to (mmm) above,

and wherein X^2 is selected from $-CH_2-$, $-CH_2CH_2-$, $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$, $-(CH_2CR^{12}R^{13})-$ and (3-6C)cycloalkenylene (for example cyclopropylene such as cyclopropylidene),

wherein each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl, provided that R^{12} and R^{13} are not both hydrogen,

and wherein X^1 is CO;

(ooo) $Z-X^2-X^1$ is hydroxy-(2-4C)alkanoyl, for example hydroxyacetyl;

(ppp) $Z-X^2-X^1$ is selected from amino-(2-4C)alkanoyl, (1-4C)alkylamino-(2-4C)alkanoyl and di-[(1-4C)alkyl]amino-(2-4C)alkanoyl (for example $Z-X^2-X^1$ is di-[(1-4C)alkyl]amino-acetyl such as dimethylaminoacetyl);

(qqq) $Z-X^2-$ is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl is linked to the carbonyl group in Formula I, by a ring carbon,

and wherein the heterocyclyl group within $Z-X^3$ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl;

(rrr) $Z-X^2-$ is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl (for example $Z-X^2$ is selected tetrahydrofuran-2-yl or tetrahydropyran-2-yl);

(sss) $Z-X^2-$ is selected from pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl is linked to X^1 in Formula I, by a ring carbon,

and wherein the heterocyclyl group within $Z\text{-}X^2$ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl; and

(ttt) $Z\text{-}X^2$ is selected from pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, homopiperidin-1-yl and homopiperazin-1-yl,

and wherein the heterocyclyl group within $Z\text{-}X^2$ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl.

A particular embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

$\mathbf{R^1}$ is selected from hydrogen, (1-6C)alkoxy, cyclopropyl-(1-4C)alkoxy, cyclobutyl-(1-4C)alkoxy, cyclopentyl-(1-4C)alkoxy, cyclohexyl-(1-6C)alkoxy, tetrahydrofuranyl-(1-4C)alkoxy and tetrahydropyranyl-(1-4C)alkoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents, or a substituent selected from hydroxy and (1-4C)alkoxy;

b is 1, 2 or 3;

each $\mathbf{R^2}$, which may be the same or different, is selected from halogeno (particularly fluoro, chloro or bromo), cyano, hydroxy, trifluoromethyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl and (1-4C)alkoxy;

$\mathbf{Q^1}$ is piperidin-4-yl;

a is 0, 1 or 2;

each W, which may be the same or different, is selected from halogeno (particularly fluoro), trifluoromethyl, hydroxy, oxo, (1-6C)alkyl, (1-6C)alkoxy, and from a group of the formula:

$$-X^8\text{-}R^{10}$$

wherein X^8 is a direct bond or is O, and R^{10} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;

$\mathbf{X^1}$ is CO; and

Z and $\mathbf{X^2}$ have any of the values hereinbefore defined;

provided that:

when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino, R^1 is hydrogen or (1-3C)alkoxy, and X^1 is CO, then a is 0 and Z is selected

from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q^6-X^9-, wherein Q^6-X^9- is as hereinbefore defined;

or a pharmaceutically acceptable salt thereof.

In this embodiment, a particular value for X^2 is a group selected from (3-6C)cycloalkylene (such as cyclopropylidene), $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$ and $-(CH_2CR^{12}R^{13})-$

wherein each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl, provided that R^{12} and R^{13} are not both hydrogen,

and wherein any CH_2 group within a (3-6C)cycloalkylene group in X^2, optionally bears on each said CH_2 or group one or more (1-4C)alkyl substituents or a substituent selected from hydroxy, (1-4C)alkoxy, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl.

In this embodiment, a particular value for Z is a group selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy and a group of the formula:

$$Q^6\text{-}X^9\text{-}$$

wherein X^9 is a direct bond or is selected from O and $N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein any heterocyclyl group in Z is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl group may be carbon or nitrogen linked to the group to which it is attached,

and wherein and wherein any CH_2 or CH_3 group within a Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl,

(2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

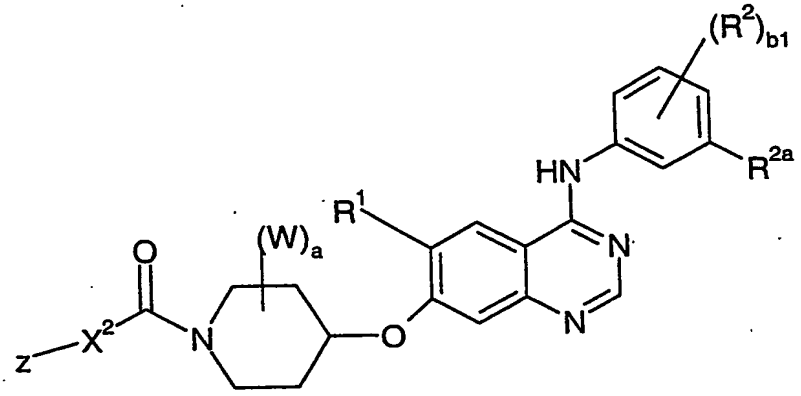
$$-X^{10}-R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl.

Another particular value for Z in this embodiment is a group selected from Z is selected from hydroxy, amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-(1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl homopiperazin-1-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, tetrahydropyranyl and 1,4-dioxanyl,

and wherein any heterocyclyl group in Z optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl and (1-4C)alkoxy.

Another embodiment of the compounds of Formula I is a quinazoline derivative of the Formula Ia:



Ia

wherein:

R^1 is selected from hydrogen, (1-6C)alkoxy, cyclopropyl-(1-4C)alkoxy, cyclobutyl-(1-4C)alkoxy, cyclopentyl-(1-4C)alkoxy, cyclohexyl-(1-6C)alkoxy, tetrahydrofuranyl-(1-4C)alkoxy and tetrahydropyranyl-(1-4C)alkoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents, or a substituent selected from hydroxy and (1-4C)alkoxy;

b1 is 0, 1 or 2;

each R^2, which may be the same or different, is selected from halogeno (particularly fluoro, chloro or bromo), cyano, hydroxy, trifluoromethyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl and (1-4C)alkoxy;

R^{2a} is halogeno (particularly fluoro, chloro or bromo, more particularly fluoro or chloro, still mare particularly chloro);

a is 0, 1 or 2;

each W, which may be the same or different, is selected from halogeno (particularly fluoro), hydroxy, (1-4C)alkyl and (1-4C)alkoxy;

X^2 is a group of the formula:

$$-(CR^{12}R^{13})_p-(Q^5)_m-(CR^{14}R^{15})_q-$$

wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

each of R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, is selected from hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q^5 is selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,

and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula:

$$Q^6\text{-}X^9\text{-}$$

wherein X^9 is a direct bond or is selected from O, $N(R^{16})$, SO_2 and $SO_2N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^{17})$, CO, -C=C- and -C≡C- wherein R^{17} is hydrogen or (1-6C)alkyl,

and wherein and wherein any CH_2 or CH_3 group within any Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^{10}\text{-}R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a quinazoline derivative of the Formula Ia as hereinbefore defined, wherein X^2 is a group selected from (3-6C)cycloalkylene (such as cyclopropylidene), $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$ and $-(CH_2CR^{12}R^{13})-$

wherein each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl, provided that R^{12} and R^{13} are not both hydrogen,

and wherein any CH_2 group within a (3-6C)cycloalkylene group in X^2, optionally bears on each said CH_2 or group one or more (1-4C)alkyl substituents or a substituent selected from hydroxy, (1-4C)alkoxy, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl.

Another embodiment of the present invention is a quinazoline derivative of the Formula 1a as hereinbefore defined, wherein X^2 is a group selected from cyclopropylidene, $-CH_2-$, $-CH_2CH_2-$, $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$ and $-(CH_2CR^{12}R^{13})-$,

wherein each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-4C)alkyl.

Another embodiment of the present invention is a quinazoline derivative of the Formula 1a as hereinbefore defined, wherein Z is selected from hydroxy, amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-(1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl homopiperazin-1-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, tetrahydropyranyl and 1,4-dioxanyl; or

the group $Z-X^2$ is selected from is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl,

homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl represented by Z-X^2 is linked to the carbonyl group in Formula Ia, by a ring carbon,

and wherein any heterocyclyl group within Z-X^3 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl.

More particularly, in Formula 1a, Z is selected from hydroxy, methoxy, ethoxy, 2-hydroxyethoxy, 2-methoxyethoxy, amino, methylamino, ethylamino, N-(2-hydroxyethyl)amino, N-(2-methoxyethyl)amino, dimethylamino, N-methyl-N-ethylamino, di-ethylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxyethyl)-N-ethylamino, N,N-di-(2-hydroxyethyl)amino, N-(2-methoxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-ethylamino, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, tetrahydrofuranyl and tetrahydropyranyl; or

the group Z-X^2 is selected from is selected from tetrahydrofuranyl and tetrahydropyranyl,

and wherein any heterocyclyl group within Z optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl and (1-4C)alkoxy.

Another embodiment of the present invention is a quinazoline derivative of the Formula 1a as hereinbefore defined, wherein:

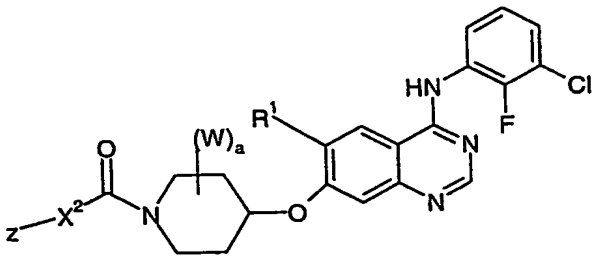
R^{2a} is fluoro or chloro (particularly chloro); and

b is 0 or 1 and R^2 is at the ortho (3-) position and is halogeno (particularly R^2 is fluoro); or

b is 0 or 1 and R^2 is at the para (4-) position and is halogeno (particularly R^2 is fluoro).

Another particular embodiment of the invention is a quinazoline of the Formula 1a as hereinbefore defined wherein the anilino group at the 4-position on the quinazoline ring is selected from 3-chloro-4-fluoroanilino and 3-chloro-2-fluoroanilino. More particularly the anilino group is 3-chloro-4-fluoroanilino.

Another embodiment of the compounds of Formula I is a quinazoline derivative of the Formula Ib:



Ib

wherein:

$\mathbf{R^1}$ is selected from hydrogen, (1-6C)alkoxy, cyclopropyl-(1-4C)alkoxy, cyclobutyl-(1-4C)alkoxy, cyclopentyl-(1-4C)alkoxy, cyclohexyl-(1-6C)alkoxy, tetrahydrofuranyl-(1-4C)alkoxy and tetrahydropyranyl-(1-4C)alkoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents, or a substituent selected from hydroxy and (1-4C)alkoxy;

a is 0, 1 or 2 (particularly a is 0);

each W, which may be the same or different, is selected from hydroxy, halogeno (particularly fluoro), (1-4C)alkyl and (1-4C)alkoxy;

$\mathbf{X^2}$ is selected from a group of the formula $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ – $(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$ and $-(CH_2CR^{12}R^{13})-$

wherein each of R^{12} and R^{13}, which may be the same or different, is selected from hydrogen and (1-4C)alkyl (particularly X^2 is CH_2);

Z is selected from hydroxy, amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-(1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl homopiperazin-1-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, tetrahydropyranyl and 1,4-dioxanyl; or

the group $Z-X^2$ is selected from is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl,

homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl represented by $Z\text{-}X^2$ is linked to the carbonyl group in Formula Ib, by a ring carbon,

and wherein any heterocyclyl group within $Z\text{-}X^3$ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl;

or a pharmaceutically acceptable salt thereof.

In an embodiment in Formula Ib, Z is selected from hydroxy, methoxy, ethoxy, 2-hydroxyethoxy, 2-methoxyethoxy, amino, methylamino, ethylamino, N-(2-hydroxyethyl)amino, N-(2-methoxyethyl)amino, dimethylamino, N-methyl-N-ethylamino, di-ethylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxyethyl)-N-ethylamino, N,N-di-(2-hydroxyethyl)amino, N-(2-methoxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-ethylamino, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, tetrahydrofuranyl and tetrahydropyranyl; or

the group $Z\text{-}X^2$ is selected from is selected from tetrahydrofuranyl and tetrahydropyranyl,

and wherein any heterocyclyl group within Z optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl and (1-4C)alkoxy.

In another embodiment in formula Ib, R^1 is selected from hydrogen methoxy, ethoxy, propyloxy, isopropyloxy, cyclopropylmethoxy, 2-hydroxyethoxy, 2-fluoroethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy (Particularly R^1 is selected from hydrogen and (1-3C)alkoxy, more particularly R^1 is (1-3C)alkoxy such as methoxy.

A particular compound of the invention is, for example, a quinazoline derivative of the Formula I selected from:

N-(3-chloro-2-fluorophenyl)-7-({1-[(dimethylamino)acetyl]piperidin-4-yl}oxy)-6-methoxyquinazolin-4-amine;

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-({1-[(2-methoxyethoxy)acetyl]piperidin-4-yl}oxy)quinazolin-4-amine;

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[1-(methoxyacetyl)piperidin-4-yl]oxy}quinazolin-4-amine;

2-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-2-oxoethanol;

N-(3-chloro-2-fluorophenyl)-7-{[1-(ethoxyacetyl)piperidin-4-yl]oxy}-6-methoxyquinazolin-4-amine;

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[1-(3-methoxypropanoyl)piperidin-4-yl]oxy}quinazolin-4-amine;

3-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-3-oxopropan-1-ol;

(2*S*)-1-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-1-oxopropan-2-ol;

(2*S*,3*S*)-1-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-3-methyl-1-oxopentan-2-ol;

4-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-2-methyl-4-oxobutan-2-ol;

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl]oxy}quinazolin-4-amine;

3-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-2,2-dimethyl-3-oxopropan-1-ol;

(3*R*,5*S*)-1-acetyl-5-{[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]carbonyl}pyrrolidin-3-ol; and

N-(3-chloro-2-fluorophenyl)-6-methoxy-7-({1-[(4-methylpiperazin-1-yl)acetyl]piperidin-4-yl}oxy)quinazolin-4-amine;

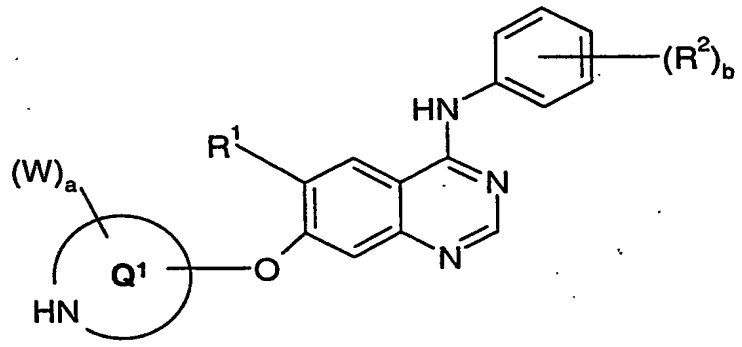
or a pharmaceutically acceptable salt thereof.

A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes include, for example, those illustrated in WO94/27965, WO 95/03283, WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980, WO 96/33981, WO 97/30034, WO 97/38994, WO01/66099, US 5,252,586, EP 520 722, EP 566 226, EP 602 851 and EP 635 507. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R^1, R^2, X^1, X^2, Q^1, W, a, b and Z have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively

necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Process (a):

For the preparation of compounds of the Formula I wherein X^1 is CO, the coupling, conveniently in the presence of a suitable base, of a quinazoline of the formula **II** or a salt thereof:



II

wherein R^1, R^2, W, a, b and Q^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an acid of the formula **III**, or a reactive derivative thereof:

$$Z\text{-}X^2\text{-}X^1\text{-}OH$$

III

wherein Z, X^1 and X^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (b) the reaction, conveniently in the presence of a suitable base, of a quinazoline of the formula **II**, or salt thereof, as hereinbefore defined in relation to Process (a), with a compound of the formula **IV**:

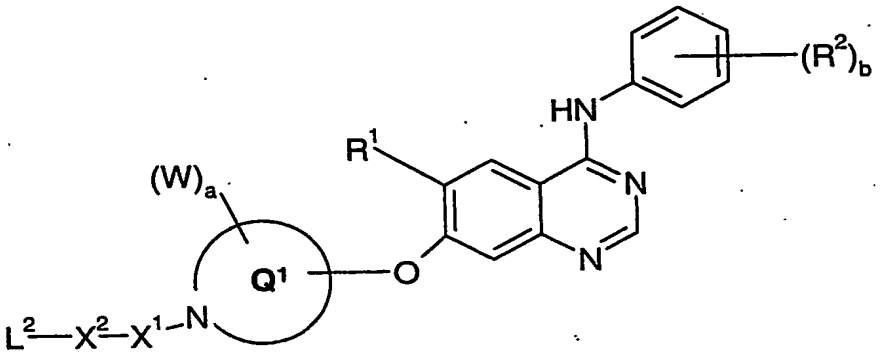
$Z\text{-}X^2\text{-}X^1\text{-}L^1$

IV

wherein L^1 is a displaceable group and Z, X^1 and X^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (c) for the preparation of those compounds of the Formula I wherein Z is linked to X^2 by nitrogen, the reaction, conveniently in the presence of a suitable base, of a compound of the formula V:



V

wherein L^2 is a displaceable group and R^1, R^2, W, X^1, X^2, a, b and Q^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the formula ZH, wherein Z is as hereinbefore defined, except that any functional group is protected if necessary;

and thereafter, if necessary (in any order):

(i) converting a quinazoline derivative of the formula I into another quinazoline derivative of the formula I;

(ii) removing any protecting group that is present by conventional means;

(iii) forming a pharmaceutically acceptable salt.

Specific conditions for the above reactions are as follows:

Process (a)

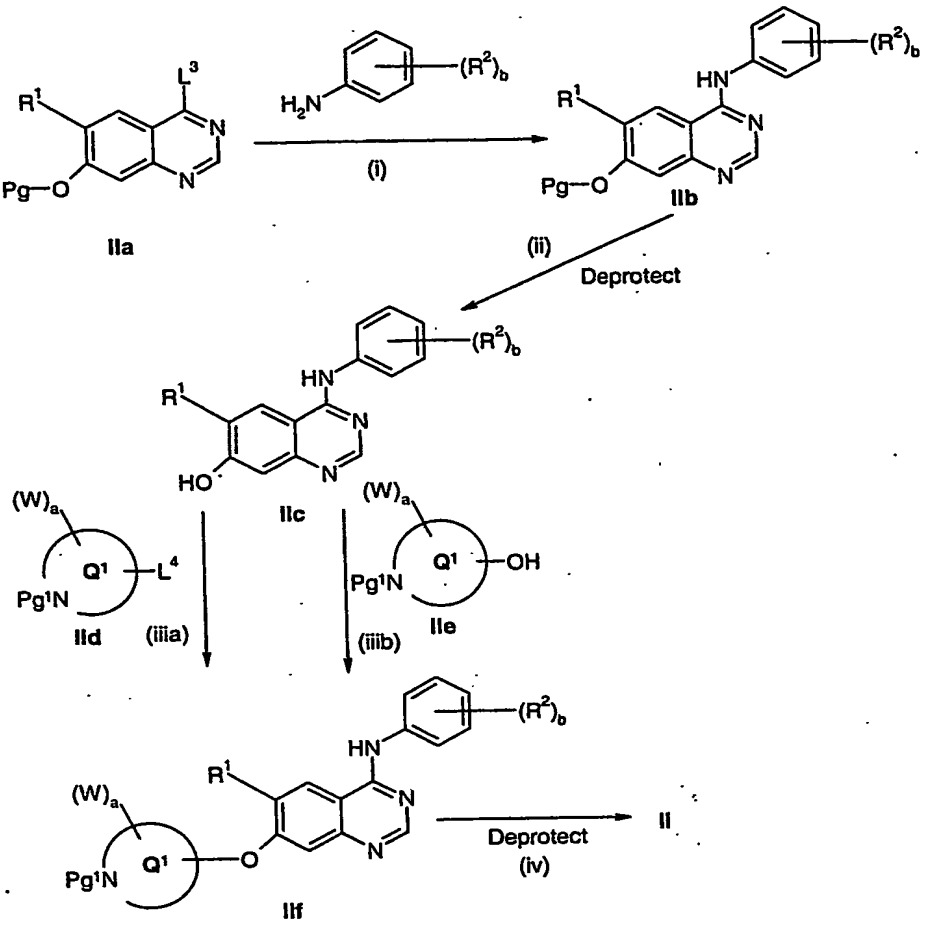
The coupling reaction is conveniently carried out in the presence of a suitable coupling agent, such as a carbodiimide, or a suitable peptide coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (HATU) or a carbodiimide such as dicyclohexylcarbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine .

The coupling reaction is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ester such as or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from 0 to 120°C, conveniently at or near ambient temperature.

By the term "reactive derivative" of the acid of the formula **III** is meant a carboxylic acid derivative that will react with the quinazoline of formula **II** to give the corresponding amide. A suitable reactive derivative of a carboxylic acid of the formula **III** is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, or N-hydroxybenzotriazole; or an acyl azide, for example an azide formed by the reaction of the acid and azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide. The reaction of such reactive derivatives of carboxylic acid with amines (such as a compound of the formula **II**) is well known in the art, for Example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature as described above.

The quinazoline of the formula **II** may be obtained by conventional procedures, for example as illustrated in *Reaction Scheme 1*:



Reaction Scheme 1

wherein R^1, R^2, Q^1, W, a and b are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means, Pg is a suitable hydroxy protecting group, Pg^1 is a suitable amino protecting group and L^3 is a displaceable group.

Conditions in *Reaction Scheme1*

Step(i): Suitable hydroxy protecting groups represented by Pg are well known in the art and include those mentioned herein, for example a lower alkanoyl group such as acetyl, or a benzyl group.

A suitable displaceable group L^3 is, for example, a halogeno (particularly chloro), alkoxy, aryloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, alkylsulfonyloxy or arylsulfonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methylthio, methanesulfonyl, methanesulfonyloxy or toluene-4-sulfonyloxy group. A particular displaceable group L^3 is chloro.

The reaction is conveniently carried out in the presence of an acid. Suitable acids include, for example hydrogen chloride gas (conveniently dissolved in a suitable solvent such as diethyl ether or dioxane) or hydrochloric acid.

Alternatively the quinazoline derivative of the formula **IIa**, wherein L^3 is halogeno (for example chloro), may be reacted with the aniline in the absence of an acid or a base. In this reaction displacement of the halogeno leaving group L^3 results in the formation of the acid HL^3 in-situ and the autocatalysis of the reaction.

Alternatively, the reaction of the quinazoline of formula **IIa** with the aniline may be carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate, or an alkali metal hydride, for example sodium hydride, an alkali metal fluoride such as cesium fluoride, or an alkali metal disilazide such as sodium hexamethyldisilazide .

The above reactions are conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide or acetonitrile. The above reactions are conveniently carried out at a temperature in the range, for example, 0 to 250°C, conveniently in the range 40 to 80°C or, preferably, at or near the reflux temperature of the solvent when used.

The aniline and the compound of the formula **IIa** are commercially available or can be prepared using conventional methods.

Step (ii):

Deprotection using well-known methods. For example when Pg is a benzyl group it may be removed by treating the compound of formula **IIb** with a suitable acid such as trifluoroacetic acid. Similarly, when Pg is a lower alkanoyl group such as acetyl it may be removed by hydrolysis using, for example ammonia, conveniently as a methanolic ammonia solution.

Step (iiia):

Suitable amino protecting groups Pg_2 are well known, for example tert-butoxycarbonyl (BOC) groups.

L^4 is a suitable displaceable group, for example as described above in relation to L^2, such as halogeno (particularly chloro or bromo), or an alkylsulfonyloxy (particularly methanesulfonyloxy) or arylsulfonyloxy (particularly toluene-4-sulfonyloxy or 4-nitrophenylsulfonyloxy) group.

The reaction of the compound of formula **IIc** with the compound of formula **IId** is conveniently carried out in the presence of a suitable base. Suitable bases include those described above in relation to step (i), such as cesium fluoride. The reaction is conveniently carried out in the presence of a suitable inert solvent, for example, a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide or acetonitrile. The above reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, conveniently in the range 40 to 80°C or, preferably, at or near the reflux temperature of the solvent when used.

Step (iiib):

An alternative to step (iiia) is the coupling of the compound of formula **IIc** with the alcohol of the formula **IIe** using the Mitsunobu coupling reaction. Suitable Mitsunobu conditions are well known and include, for example, reaction in the presence of a suitable tertiary phosphine and a di-alkylazodicarboxylate in an organic solvent such as THF, or suitably dichloromethane and in the temperature range 0°C to 60°C, but suitably at or near ambient temperature. A suitable tertiary phosphine includes for example tri-n-butylphosphine or particularly tri-phenylphosphine. A suitable di-alkylazodicarboxylate includes, for example, diethyl azodicarboxylate (DEAD) or suitably di-tert-butyl azodicarboxylate (DTAD). Details of Mitsunobu reactions are contained in Tet. Letts., 31, 699, (1990); The Mitsunobu Reaction, D.L.Hughes, Organic Reactions, 1992, Vol.42, 335-656 and Progress in the Mitsunobu Reaction, D.L.Hughes, Organic Preparations and Procedures International, 1996, Vol.28, 127-164.

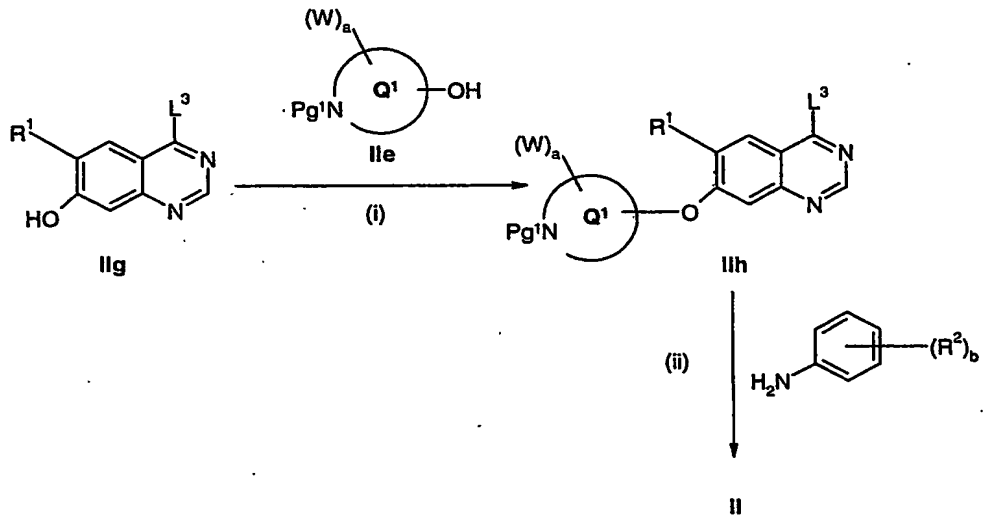
The compounds of the formulae **IId** and **IIe** are commercially available or can be prepared using conventional methods.

Step (iv):

Removal of the amino protecting group Pg_1 using well known methods. For example when Pg_1 is a BOC group, by treatment with a suitable acid such as trifluoroacetic acid.

In an alternative route to that shown in *Reaction Scheme 1*, the aniline in step (i) may be reacted with the unprotected variant of the compound of the formula **IIa** (i.e. Pg is hydrogen), to give the compound of formula **IIc** directly.

The compound of formula **II** may also be prepared according to *Reaction Scheme 2*:



Reaction Scheme 2

wherein R^1, R^2, Q^1, W, a, b, L^3 and Pg^1 are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means.

Conditions in *Reaction Scheme2*

Step (i):

Coupling under Mitsunobu conditions as described above in relation to step (iiib) in *Reaction Scheme 1*.

Step (ii):

The reaction is conveniently carried out in the presence of an acid. Suitable acids include, for example hydrogen chloride gas (conveniently dissolved in a suitable solvent such as diethyl ether or dioxane) or hydrochloric acid. The reaction is conveniently carried out in a suitable inert solvent, for example as described in step (i) of *Reaction Scheme 1*.

The quinazoline of the formula **IIg** is commercially available or can be prepared using conventional methods.

Process (b)

A suitable displaceable group L^1 includes for example halogeno such as chloro.

The reaction is conveniently performed in the presence of a suitable base, for example, conveniently in the presence of a suitable base, for example an organic amine base such as,

for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, or an alkali metal hydride, for example sodium hydride, or an alkali metal disilazide such as sodium hexamethyldisilazide.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

The compound of the formula **IV** are commercially available compounds or they are known in the literature, or they can be can be prepared by standard processes known in the art.

Process (c):

A suitable displaceable group represented by L^2 includes, for example a halogeno or a sulfonyloxy group, for example chloro, bromo, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular group L^2 is chloro.

The reaction is conveniently performed in the presence of a suitable base, for example one of the bases described in relation to Process (b).

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an ester such as ethyl acetate, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

The compound of formula **V** used as starting material may be prepared by, for example, reacting, conveniently in the presence of a suitable base, a quinazoline of the formula **II**, or salt thereof, as hereinbefore defined in relation to Process (a), with a compound of the formula **Va**:

$$L^2\text{-}X^2\text{-}X^1\text{-}L^5$$

Va

wherein X^1 and X^2 are as hereinbefore defined, and L^2 and L^5 are suitable displaceable groups, provided that L^5 is more labile than L^2.

Suitable displaceable groups represented by L^2 and L^5 include for example halogeno such as chloro.

The reaction is conveniently carried out in the presence of a suitable base and in a suitable inert solvent or diluent as defined above for the reaction of the quinazoline of formula V with the compound of the formula ZH.

The compounds of the formulae ZH and Va are commercially available compounds or they are known in the literature, or they can be can be prepared by standard processes known in the art.

Conveniently, in an embodiment of Process (c), a quinazoline of Formula I may be prepared directly from a quinazoline of formula II by reacting the quinazoline of formula II with a compound of formula Va and then reacting the resultant product directly with the compound of the formula ZH without isolating the compound of formula V. This reaction enables the quinazoline of Formula I to be prepared in a single reaction vessel starting with the quinazoline of formula II.

The quinazoline derivative of the Formula I may be obtained from the above processes in the form of the free base or alternatively it may be obtained in the form of a salt, an acid addition salt. When it is desired to obtain the free base from a salt of the compound of Formula I, the salt may be treated with a suitable base, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or by treatment with ammonia for example using a methanolic ammonia solution such as 7N ammonia in methanol.

The protecting groups used in the processes above may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are

given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy-lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); lower alkanoyloxyalkyl groups (for example pivaloyloxymethyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl. For example a tert butoxycarbonyl protecting group may be removed from an amino group by an acid catalysed hydrolysis using trifluoroacetic acid.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

As mentioned hereinbefore some of the compounds according to the present invention may contain one of more chiral centers and may therefore exist as stereoisomers (for example when Q^1 is piperidin-3-yl). Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for example by fractional crystallisation, resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash

chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. When a specific stereoisomer is isolated it is suitably isolated substantially free for other stereoisomers, for example containing less than 20%, particularly less than 10% and more particularly less than 5% by weight of other stereoisomers.

In the section above relating to the preparation of the quinazoline derivative of Formula I, the expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

Certain intermediates used in the processes described above are novel and form a further feature of the present invention. According to a further aspect of the present invention there is provided a quinazoline derivative of the formula **II** as hereinbefore defined wherein a is 2 and each R^2, which may be the same or different, is halogeno (particularly selected from fluoro and chloro) and wherein the R^2 groups are located at the ortho (2-) and meta (3-) positions on the aniline ring; or a salt thereof. A particular compound of the formula **II** is a compound of the formula **II** wherein the anilino group is 3-chloro-2-fluoroanilino. The intermediate may be in the form of a salt of the intermediate. Such salts need not be a pharmaceutically acceptable salt. For example it may be useful to form prepare an intermediate in the form of a pharmaceutically non-acceptable salt if, for example, such salts are useful in the manufacture of a compound of Formula I.

Biological Assays

The inhibitory activities of compounds were assessed in non-cell based protein tyrosine kinase assays as well as in cell based proliferation assays before their *in vivo* activity was assessed in Xenograft studies.

a) Protein Tyrosine Kinase phosphorylation Assays

This test measures the ability of a test compound to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by EGFR tyrosine kinase enzyme.

Recombinant intracellular fragments of EGFR, erbB2 and erbB4 (accession numbers X00588, X03363 and L07868 respectively) were cloned and expressed in the baculovirus/Sf21 system. Lysates were prepared from these cells by treatment with ice-cold lysis buffer (20mM N-2-hydroxyethylpiperizine-N'-2-ethanesulfonic acid (HEPES) pH7.5, 150mM NaCl, 10% glycerol, 1% Triton X-100, 1.5mM $MgCl_2$, 1mM ethylene glycol-bis(β-aminoethyl ether) N',N',N',N'-tetraacetic acid (EGTA), plus protease inhibitors and then cleared by centrifugation.

Constitutive kinase activity of these recombinant proteins was determined by their ability to phosphorylate a synthetic peptide (made up of a random co-polymer of Glutamic Acid, Alanine and Tyrosine in the ratio of 6:3:1). Specifically, Maxisorb™ 96-well immunoplates were coated with synthetic peptide (0.2μg of peptide in a 200μl phosphate buffered saline (PBS) solution and incubated at 4°C overnight). Plates were washed in 50mM HEPES pH 7.4 at room temperature to remove any excess unbound synthetic peptide. EGFR or erbB2 activities were assessed by incubation in peptide coated plates for 20 minutes at room temperature in 100mM HEPES pH 7.4 at room temperature, adenosine trisphosphate (ATP) at Km concentration for the respective enzyme, 10mM $MnCl_2$, 0.1mM Na_3VO_4, 0.2mM DL-dithiothreitol (DTT), 0.1% Triton X-100 with test compound in DMSO (final concentration of 2.5%). Reactions were terminated by the removal of the liquid components of the assay followed by washing of the plates with PBS-T (phosphate buffered saline with 0.5% Tween 20).

The immobilised phospho-peptide product of the reaction was detected by immunological methods. Firstly, plates were incubated for 90 minutes at room temperature with anti-phosphotyrosine primary antibodies that were raised in the mouse (4G10 from Upstate Biotechnology). Following extensive washing, plates were treated with Horseradish Peroxidase (HRP) conjugated sheep anti-mouse secondary antibody (NXA931 from Amersham) for 60 minutes at room temperature. After further washing, HRP activity in each well of the plate was measured colorimetrically using 22'-Azino-di-[3-ethylbenzthiazoline sulfonate (6)] diammonium salt crystals (ABTS™ from Roche) as a substrate.

Quantification of colour development and thus enzyme activity was achieved by the measurement of absorbance at 405nm on a Molecular Devices ThermoMax microplate reader.

Kinase inhibition for a given compound was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of phosphorylation in this assay. The range of phosphorylation was calculated from the positive (vehicle plus ATP) and negative (vehicle minus ATP) control values.

b) EGFR driven KB cell proliferation assay

This assay measures the ability of a test compound to inhibit the proliferation of KB cells (human naso-pharangeal carcinoma obtained from the American Type Culture Collection (ATCC)).

KB cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal calf serum, 2 mM glutamine and non-essential amino acids at 37°C in a 7.5% CO_2 air incubator. Cells were harvested from the stock flasks using Trypsin/ethylaminediaminetetraacetic acid (EDTA). Cell density was measured using a haemocytometer and viability was calculated using trypan blue solution before being seeded at a density of $1.25x10^3$ cells per well of a 96 well plate in DMEM containing 2.5% charcoal stripped serum, 1mM glutamine and non-essential amino acids at 37°C in 7.5% CO_2 and allowed to settle for 4 hours.

Following adhesion to the plate, the cells are treated with or without EGF (final concentration of 1ng/ml) and with or without compound at a range of concentrations in dimethylsulfoxide (DMSO) (0.1% final) before incubation for 4 days. Following the incubation period, cell numbers were determined by addition of 50µl of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) for 2 hours. MTT solution was then tipped off, the plate gently tapped dry and the cells dissolved upon the addition of 100µl of DMSO.

Absorbance of the solubilised cells was read at 540nm using a Molecular Devices ThermoMax microplate reader. Inhibition of proliferation was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus EGF) and negative (vehicle minus EGF) control values.

c) Clone 24 phospho-erbB2 cell assay

This immunofluorescence end point assay measures the ability of a test compound to inhibit the phosphorylation of erbB2 in a MCF7 (breast carcinoma) derived cell line which was generated by transfecting MCF7 cells with the full length erbB2 gene using standard

methods to give a cell line that overexpresses full length wild type erbB2 protein (hereinafter 'Clone 24' cells).

Clone 24 cells were cultured in Growth Medium (phenol red free Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal bovine serum, 2 mM glutamine and 1.2mg/ml G418) in a 7.5% CO_2 air incubator at 37°C. Cells were harvested from T75 stock flasks by washing once in PBS (phosphate buffered saline, pH7.4, Gibco No. 10010-015) and harvested using 2mls of Trypsin (1.25mg/ml) / ethylaminediaminetetraacetic acid (EDTA) (0.8mg/ml) solution. The cells were resuspended in Growth Medium. Cell density was measured using a haemocytometer and viability was calculated using Trypan Blue solution before being further diluted in Growth Medium and seeded at a density of $1x10^4$ cells per well (in 100ul) into clear bottomed 96 well plates (Packard, No. 6005182).

3 days later, Growth Medium was removed from the wells and replaced with 100ul Assay Medium (phenol red free DMEM, 2mM glutamine, 1.2mg/ml G418) either with or without erbB inhibitor compound. Plates were returned to the incubator for 4hrs and then 20µl of 20% formaldehyde solution in PBS was added to each well and the plate was left at room temperature for 30 minutes. This fixative solution was removed with a multichannel pipette, 100µl of PBS was added to each well and then removed with a multichannel pipette and then 50µl PBS was added to each well. Plates were then sealed and stored for up to 2 weeks at 4°C.

Immunostaining was performed at room temperature. Wells were washed once with 200µl PBS / Tween 20 (made by adding 1 sachet of PBS / Tween dry powder (Sigma, No. P3563) to 1L of double distilled H_2O) using a plate washer then 200µl Blocking Solution (5% Marvel dried skimmed milk (Nestle) in PBS /Tween 20) was added and incubated for 10 minutes. Blocking Solution was removed using a plate washer and 200µl of 0.5% Triton X-100 / PBS was added to permeabalise the cells. After 10 minutes, the plate was washed with 200µl PBS / Tween 20 and then 200µl Blocking Solution was added once again and incubated for 15 minutes. Following removal of the Blocking Solution with a plate washer, 30µl of rabbit polyclonal anti-phospho ErbB2 IgG antibody (epitope phospho-Tyr 1248, SantaCruz, No. SC-12352-R), diluted 1:250 in Blocking Solution, was added to each well and incubated for 2 hours. Then this primary antibody solution was removed from the wells using a plate washer followed by two 200µl PBS / Tween 20 washes using a plate washer. Then 30µl of Alexa-Fluor 488 goat anti-rabbit IgG secondary antibody (Molecular Probes, No. A-11008), diluted 1:750 in Blocking Solution, was added to each well. From now onwards, wherever possible, plates were protected from light exposure, at this stage by sealing with black

backing tape. The plates were incubated for 45 minutes and then the secondary antibody solution was removed from the wells followed by two 200ul PBS / Tween 20 washes using a plate washer. Then 100µl PBS was added to each plate, incubated for 10 minutes and then removed using a plate washer. Then a further 100µl PBS was added to each plate and then, without prolonged incubation, removed using a plate washer. Then 50µl of PBS was added to each well and plates were resealed with black backing tape and stored for up to 2 days at 4°C before analysis.

The Fluorescence signal is each well was measured using an Acumen Explorer Instrument (Acumen Bioscience Ltd.), a plate reader that can be used to rapidly quantitate features of images generated by laser-scanning. The instrument was set to measure the number of fluorescent objects above a pre-set threshold value and this provided a measure of the phosphorylation status of erbB2 protein. Fluorescence dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Inhibition of erbB2 phosphorylation was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of erbB2 phosphorylation signal.

d) *In vivo* Xenograft assay

This assay measures the ability of a test compound to inhibit the growth of a LoVo tumour (colorectal adenocarcinoma obtained from the ATCC) in Female Swiss athymic mice (Alderley Park, *nu/nu* genotype).

Female Swiss athymic (*nu/nu* genotype) mice were bred and maintained in Alderley Park in negative pressure Isolators (PFI Systems Ltd.). Mice were housed in a barrier facility with 12hr light/dark cycles and provided with sterilised food and water *ad libitum*. All procedures were performed on mice of at least 8 weeks of age. LoVo tumour cell (colorectal adenocarcinoma obtained from the ATCC) xenografts were established in the hind flank of donor mice by sub cutaneous injections of $1x10^7$ freshly cultured cells in 100µl of serum free media per animal. On day 5 post-implant, mice were randomised into groups of 7 prior to the treatment with compound or vehicle control that was administered once daily at 0.1ml/10g body weight. Tumour volume was assessed twice weekly by bilateral Vernier calliper measurement, using the formula (length x width) x $\sqrt{}$(length x width) x (π/6), where length was the longest diameter across the tumour, and width was the corresponding perpendicular. Growth inhibition from start of study was calculated by comparison of the mean changes in

tumour volume for the control and treated groups, and statistical significance between the two groups was evaluated using a Students *t* test.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

Test (a):- IC_{50} in the range, for example, 0.001 - 1 μM;

Test (b):- IC_{50} in the range, for example, 0.001 - 5 μM;

Test (c):- IC_{50} in the range, for example, 0.01 - 5 μM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day;

No physiologically unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral

administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a quinazoline derivative of the formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a quinazoline derivative of the formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties that are believed to arise from their erbB family receptor tyrosine kinase inhibitory activity, particularly inhibition of the EGF receptor (erbB1) tyrosine kinase. Furthermore, certain of the compounds according to the present invention possess substantially better potency against the EGF receptor tyrosine kinase, than against other tyrosine kinase enzymes, for example erbB2. Such compounds possess sufficient potency against the EGF receptor tyrosine kinase that they may be used in an amount sufficient to inhibit EGF receptor tyrosine kinase whilst demonstrating little, or significantly lower, activity against other tyrosine kinase enzymes such as erbB2. Such compounds are likely to be useful for the selective inhibition of EGF receptor tyrosine kinase and are likely to be useful for the effective treatment of, for example EGF driven tumours.

Accordingly, the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by erbB receptor tyrosine kinases (especially EGF receptor tyrosine kinase), i.e. the compounds may be used to produce an erbB receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for the

treatment of malignant cells characterised by inhibition of one or more of the erbB family of receptor tyrosine kinases. Particularly the compounds of the invention may be used to produce an anti-proliferative and/or pro-apoptotic and/or anti-invasive effect mediated alone or in part by the inhibition of erbB receptor tyrosine kinases. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to inhibition of one or more of the erbB receptor tyrosine kinases, such as EGF and/or erbB2 and/or erbB4 receptor tyrosine kinases (especially EGF receptor tyrosine kinase) that are involved in the signal transduction steps which drive proliferation and survival of these tumour cells. Accordingly the compounds of the present invention are expected to be useful in the treatment of psoriasis, benign prostatic hyperplasia (BPH), atherosclerosis and restenosis and/or cancer by providing an anti-proliferative effect, particularly in the treatment of erbB receptor tyrosine kinase sensitive cancers. Such benign or malignant tumours may affect any tissue and include non-solid tumours such as leukaemia, multiple myeloma or lymphoma, and also solid tumours, for example bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancers.

According to this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to a further aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as

defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of erbB receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR), that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the erbB family of receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR), that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of those tumours which are sensitive to inhibition of erbB receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR), that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a EGFR and/or erbB2 and/or erbB4 (especially a EGFR) tyrosine kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a EGFR and/or an erbB2 and or an erbB4 (especially a EGFR) tyrosine kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in providing a EGFR and/or erbB2 and/or erbB4 (especially a EGFR) tyrosine kinase inhibitory effect.

According to a further feature of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a selective EGFR tyrosine kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a selective EGFR tyrosine kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in providing a selective EGFR tyrosine kinase inhibitory effect.

By "a selective EGFR kinase inhibitory effect" is meant that the quinazoline derivative of Formula I is more potent against EGF receptor tyrosine kinase than it is against other kinases. In particular some of the compounds according to the invention are more potent against EGF receptor kinase than it is against other tyrosine kinases such as other erbB receptor tyrosine kinases such erbB2. For example a selective EGFR kinase inhibitor according to the invention is at least 5 times, preferably at least 10 times more potent against EGF receptor tyrosine kinase than it is against erbB2 tyrosine kinase, as determined from the relative IC_{50} values in suitable assays. For example, by comparing the IC_{50} value from the KB cell assay (a measure of the EGFR tyrosine kinase inhibitory activity) with the IC_{50} value from the Clone 24 phospho-erbB2 cell assay (a measure of erb-B2 tyrosine kinase inhibitory activity) for a given test compound as described above.

According to a further aspect of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer (for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer).

According to a further feature of this aspect of the invention there is provided a method for treating a cancer (for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer) in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of a cancer (for example selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer).

As mentioned above the size of the dose required for the therapeutic or prophlyactic treatment of a particular disease will necessarily be varied depending upon, amongst other things, the host treated, the route of administration and the severity of the illness being treated.

The anti-proliferative treatment/tyrosine kinase inhibitory effect defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example other inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the Formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of the erbB receptor tyrosine protein kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulfate or sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and / or analytical LCMS, and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at the operating frequency of the NMR apparatus used (300 or 400 MHz), using perdeuterio dimethyl sulfoxide (DMSO-d_6) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms;

(x) mass spectra (MS) were run using a Waters or Micromass electrospray LC-MS in positive or negative ion mode; values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$;

(xi) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example; and

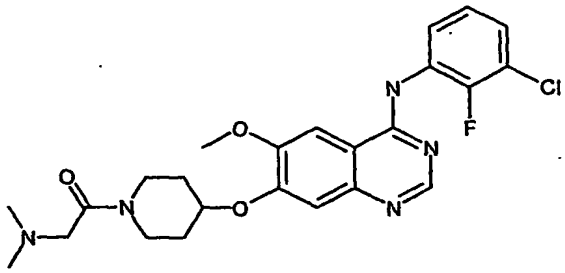
(xii) the following abbreviations have been used:

HATU O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-Tetramethyluronium Hexafluoro-Phosphate;

DMA	*N,N*-dimethylacetamide;
DMSO	dimethylsulfoxide;
IPA	Isopropyl alcohol;
TFA	trifluoroacetic acid; and
EtOAc	ethyl acetate.

Example 1

***N*-(3-Chloro-2-fluorophenyl)-7-({1-[(dimethylamino)acetyl]piperidin-4-yl}oxy)-6-methoxyquinazolin-4-amine**



N,N-Dimethylaminoacetyl chloride hydrochloride (100mg) was added portionwise to a stirred solution of *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride (250mg, 0.57mmol) and diisopropylethylamine (300 µl) in methylene chloride (25 ml) at 0°C. The reaction mixture was allowed to stir for 2 hours to room temperature. The reaction mixture was washed with saturated sodium bicarbonate solution (25ml), dried ($MgSO_4$), filtered and evaporated. The residues were purified by column chromatography eluting with increasingly polar mixtures of methylene chloride/methanol (100/0 to 90/10), followed by methylene chloride/methanol (saturated with ammonia) (90/10). The fractions containing the desired product were combined and evaporated under vacuum to give the title product as a white foam (0.125g, 45%); ^{1}H NMR Spectrum: (DMSO d_6) 1.50-1.65 (m, 1H); 1.65-1.80 (m, 1H); 1.95-2.15 (m, 2H); 2.25 (s, 6H); 3.10-3.50 (m, 4H); 3.75-4.05 (m, 2H); 3.95 (s, 3H); 4.90 (m, 1H); 7.30 (m, 1H); 7.35 (s, 1H); 7.40-7.60 (m, 2H); 7.85 (s, 1H); 8.40 (s, 1H); 9.65 (s, 1H); Mass Spectrum: $(M+H)^+$ 488.

The *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride used as starting material was prepared as follows:

4.0M HCl in Dioxane (4.0 ml) was added to a stirred suspension of 7-(benzyloxy)-4-chloro-6-methoxyquinazoline (CAS Registry No162364-72-9) (60 g, 0.2 mol) and 3-chloro-2-fluoroaniline (31.96 g, 0.22 mol) in acetonitrile (1200 ml). The reaction mixture was heated at 80^{0}C for 1 hour then left to stand overnight. Acetonitrile (500 ml) was added and the resulting precipitate filtered, washed with acetonitrile (3 x 500 ml) and dried under vacuum to give 7-(benzyloxy)-*N*-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride as a beige solid (85.45 g, 96%); ^{1}H NMR Spectrum: (DMSO d_6) 4.02 (s, 3H), 5.35 (s, 2H), 7.30-7.60 (m, 9H), 7.65 (m, 1H), 8.38 (s, 1H), 8.85 (s, 1H), 11.8 (s, 1H); Mass Spectrum: $(M+H)^+$ 410.

A solution of 7-(benzyloxy)-*N*-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride (85.45g, 0.192mol) in trifluoroacetic acid (300 ml) was heated at 80°C for 1 hour. The reaction mixture was the evaporated to dryness and the residues re-dissolved in methanol (200ml). This solution was then added dropwise to a stirred aqueous solution of saturated sodium bicarbonate (500ml). The resulting precipitate was collected by filtration, washed with acetonitrile and dried under vacuum. The resulting solids were then purified by hot (100°C) trituration with a mixture of butanone (500 ml) and MeOH (100ml), filtered and dried to 4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-ol as a cream solid (45 g, 73%); ^{1}H NMR Spectrum: (DMSO d_6): 3.98 (s, 3H), 7.10 (s, 1H), 7.25-7.30 (m, 1H), 7.40-7.50 (m, 1H), 7.50-7.60 (m, 1H), 7.80 (s, 1H), 8.30 (s, 1H), 9.55 (s, 1H), 10.32 (s, 1H); Mass Spectrum: $(M+H)^+$ 320.

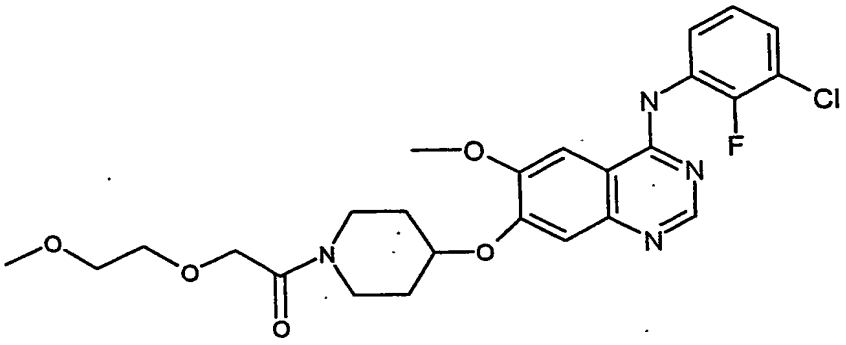
4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-ol (500 mg, 1.565 mmol) was dissolved in DMA (20 ml). *tert*-Butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (CAS Registry Number:141699-59-4) (436.6 mg, 1.565 mmol) and cesium fluoride (236.3 mg, 1.565 mmol) were added, and the mixture was heated to 60°C with stirring. After 18 hours, *tert*-butyl 4-methanesulfonyloxypiperidine-1-carboxylate and cesium fluoride were again added in the same quantities to the reaction mixture and heating was continued at 60°C for a further 18 hours. The solvent was evaporated, and the residue was partitioned between saturated aqueous sodium bicarbonate solution (50ml) and EtOAc (2x50ml). The organics were combined, dried over $MgSO_4$ and evaporated. The resulting product was then purified by column chromatography eluting with increasingly polar mixtures of methylene chloride/EtOAc (100/0 to 0/100). The fractions containing the desired product were combined and evaporated under vacuum to give *tert*-butyl 4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidine-1-carboxylate as a colourless foam (757 mg, 96%); ^{1}H NMR Spectrum: (DMSO-d_6): 1.52 (s, 9H), 1.60-1.80 (m, 2H), 2.02-2.20 (m, 2H), 3.20-3.45 (m, 2H), 3.75-3.92 (m, 2H), 4.05 (s, 3H), 4.95 (m, 1H), 7.32-7.45 (m, 2H), 7.55-7.70 (m, 2H), 7.92 (s, 1H), 8.50 (s, 1H), 9.73 (s, 1H); Mass Spectrum: $(M+H)^+$ 503.

Trifluoroacetic acid (50 ml) was added to a solution of *tert*-butyl 4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidine-1-carboxylate (750 mg, 1.49 mmol) in methylene chloride (1 ml) and triethylsilane (1 ml) and the solution stirred for 1 hour. The reaction mixture was then evaporated under reduced pressure and the residues re-dissolved in EtOAc (5 ml). This solution was then treated with 1M HCl/diethylether (1 ml) followed by more diethylether (50 ml) to give a white precipitate. The resulting solids were collected

following centrifugation and dried under vacuum to give *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride as a white solid (750 mg); ^{1}H NMR Spectrum: (DMSO-d_6): 2.00-2.20 (m, 2H), 2.25-2.45 (m, 2H), 3.15-3.50 (m, 4H), 4.15 (s, 3H), 5.02 (m, 1H), 7.48 (m, 1H), 7.60-7.85 m, 3H), 8.35 (s, 1H), 8.85 (s, 1H), 9.56 (bs, 2H); Mass Spectrum : $(M+H)^+$ 403.

Example 2

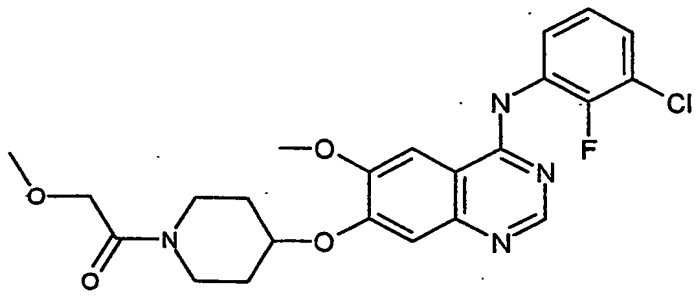
***N*-(3-Chloro-2-fluorophenyl)-6-methoxy-7-({1-[(2-methoxyethoxy)acetyl]piperidin-4-yl}oxy)quinazolin-4-amine**



N-(3-Chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride (300 mg), diisopropylethylamine (0.45 ml) and 2-(2-methoxyethoxy)acetyl chloride (0.105 g) were stirred in methylene chloride (9 ml) for 2.5 hours. Methylene chloride (20 ml) was added and the organic layer was washed with aqueous sodium hydroxide (2M, 30 ml) and water (30 ml). The resulting product was purified by flash column chromatography eluting with methanol (3%) and methylene chloride (97%) gave a foam. This was re-precipitated by stirring in diethyl ether (20 ml) to give the title product as a white solid (0.110 g); ^{1}H NMR Spectrum : (DMSO d_6 373K) 1.73 (m, 2H), 2.02 (m, 2H), 3.29 (s, 3H), 3.42 (m, 2H), 3.51 (t, J=7Hz, 2H), 3.60 (t, J=9Hz, 2H), 3.78 (m, 2H), 3.96 (s, 3H), 4.17 (s, 2H), 4.87 (m, 1H), 7.27 (m, 1H), 7.33 (s, 1H), 7.42 (m, 1H), 7.58 (m, 1H), 7.85 (s, 1H), 8.39 (s, 1H), 9.29 (br s, 1H); Mass Spectrum : $(M+H)^+$ 519.

Example 3

***N*-(3-Chloro-2-fluorophenyl)-6-methoxy-7-{[1-(methoxyacetyl)piperidin-4-yl]oxy}quinazolin-4-amine**

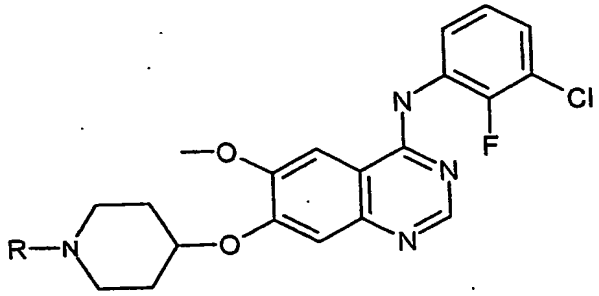


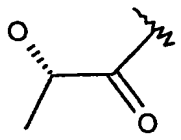
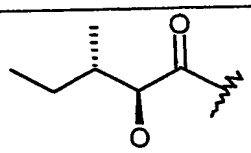
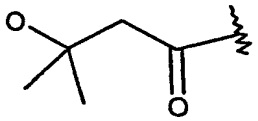
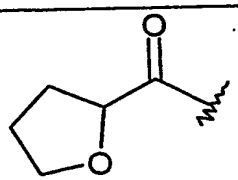
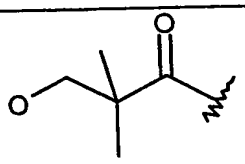
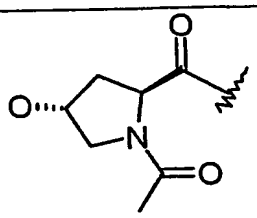
HATU (0.24g) was added to a solution of *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride (250 mg), diisopropylethylamine (0.37 ml) and methoxyacetic acid (0.054 g) in methylene chloride (9 ml) and the mixture was stirred at room temperature for 2.5 hours. Methylene chloride (20 ml) was added and the organic layer was washed with aqueous sodium hydroxide (2M, 30 ml) and water (30 ml). The resulting product was purified by flash column chromatography eluting with methanol (3%) and methylene chloride (97%) to give a foam. This was re-precipitated by stirring in diethyl ether (20 ml) to give the title product as a white solid (0.200 g); ^{1}H NMR Spectrum : (DMSO d_6 373K) 1.73 (m, 2H), 2.02 (m, 2H), 3.37 (s, 3H), 3.41 (m, 2H), 3.77 (m, 2H), 3.98 (s, 3H), 4.09 (s, 2H), 4.85 (m, 1H), 7.26 (m, 1H), 7.30 (s, 1H), 7.39 (m, 1H), 7.59 (m, 1H), 7.81 (s, 1H), 8.38 (s, 1H), 9.34 (br s, 1H); Mass Spectrum : $(M+H)^+$ 475.

Example 4

Using a similar procedure to that described in Example 3, *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride was coupled with the appropriate carboxylic to give the compounds shown in Table I:

Table 1



No. and Note	R
[1]	hydroxyacetyl
[2]	ethoxyacetyl
[3]	3-methoxypropanoyl
[4]	3-hydroxypropanoyl
[5]	
[6]	
[7]	
[8]	
[9]	
[10]	

Notes:

In Table 1 ≈ refers to the point of attachment of the carbonyl group in Table 1 to the nitrogen in the piperidin-4-yl group.

[1] 2-[4-({4-[3-Chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-2-oxoethanol (0.170 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.78 (m, 2H), 2.02 (m, 2H), 3.42 (m, 2H), 3.75 (m, 2H), 3.97 (s, 3H), 4.11 (s, 2H), 4.84 (m, 1H), 7.25 (m, 1H), 7.31 (s, 1H), 7.40 (m, 1H), 7.50-7.67 (m, 2H), 7.82 (s, 1H), 8.38 (s, 1H), 9.31 (br s, 1H); Mass Spectrum: $(M+H)^+$ 461.

[2] *N*-(3-Chloro-2-fluorophenyl)-7-{[1-(ethoxyacetyl)piperidin-4-yl]oxy}-6-methoxyquinazolin-4-amine as a white solid (0.185 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.18 (t, J=8Hz, 3H), 1.74 (m, 2H), 2.03 (m, 2H), 3.41 (m, 2H), 3.52 (q, J=8Hz, 2H), 3.79 (m, 2H), 3.98 (s, 3H), 4.12 (s, 2H), 4.84 (m, 1H), 7.23 (m, 1H), 7.32 (s, 1H), 7.42 (m, 1H), 7.58 (m, 1H), 7.81 (s, 1H), 8.38 (s, 1H), 9.30 (br s, 1H); Mass Spectrum: $(M+H)^+$ 489.

[3] *N*-(3-Chloro-2-fluorophenyl)-6-methoxy-7-{[1-(3-methoxypropanoyl)piperidin-4-yl]oxy}quinazolin-4-amine (0.155 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.73 (m, 2H), 2.01 (m, 2H), 2.62 (t, J=9Hz, 2H), 3.28 (s, 3H), 3.41 (m, 2H), 3.60 (t, J=9Hz, 2H), 3.79 (m, 2H), 3.97 (s, 3H), 4.82 (m, 1H), 7.24 (m, 1H), 7.30 (s, 1H), 7.40 (m, 1H), 7.58 (m, 1H), 7.81 (s, 1H), 8.38 (s, 1H), 9.30 (br s, 1H); Mass Spectrum : $(M+H)^+$ 489.

[4] 3-[4-({4-[3-Chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-3-oxopropan-1-ol (0.061 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.72 (m, 2H), 2.01 (m, 2H), 2.62 (t, J=8Hz, 2H), 3.40 (m, 2H), 3.71 (m, 2H), 3.80 (m, 2H), 3.96 (s, 3H), 4.13 (t, J=5Hz, 1H), 4.83 (m, 1H), 7.28 (m, 1H), 7.31 (s, 1H), 7.42 (m, 1H), 7.59 (m, 1H), 7.83 (s, 1H), 8.39 (s, 1H), 9.29 (br s, 1H); Mass Spectrum: $(M+H)^+$ 475.

[5] Following the coupling reaction the product was purified by flash column chromatography eluting with methylene chloride / 7N ammonia solution in methanol (98.6/1.4) to give foam. This was re-precipitated by stirring in diethyl ether (20ml) to give (2*S*)-1-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-1-oxopropan-2-ol as a white solid (0.092 g); ^{1}H NMR Spectrum : (DMSO d_6 373K) 1.25 (d, J=5Hz, 3H), 1.73 (m, 2H), 2.05 (m, 2H), 3.43 (m, 2H), 3.82 (m, 2H), 3.98 (s, 3H), 4.51 (m, 2H), 4.87 (m, 1H), 7.28 (m, 1H), 7.32 (s, 1H), 7.42 (m, 1H), 7.61 (m, 1H), 7.82 (s, 1H), 8.40 (s, 1H), 9.32 (br s, 1H); Mass Spectrum : $(M+H)^+$ 475.

[6] Following the coupling reaction, the product was purified by flash column chromatography eluting with methylene chloride / 7N ammonia solution in methanol (98/2) gave a foam. This was re-precipitated by stirring in diethyl ether (20 ml) to give (2*S*,3*S*)-1-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-3-methyl-1-oxopentan-2-ol as a white solid (0.244 g); ^{1}H NMR Spectrum: (DMSO d_6) 0.78 (d, J=7Hz, 3H), 0.91 (t, J=7Hz, 3H), 1.21 (m, 1H), 1.44 (m, 1H), 1.61 (m, 3H), 2.05 (m, 2H), 3.40 (m, 2H), 3.79 (m, 1H), 3.95 (s, 3H), 4.00 (m, 1H), 4.28 (m, 1H), 4.43 (m, 1H), 4.93 (m, 1H), 7.29 (m, 1H), 7.36 (s, 1H), 7.48 (m, 1H), 7.53 (m, 1H), 7.83 (s, 1H), 8.39 (s, 1H), 9.63 (br s, 1H); Mass Spectrum : $(M+H)^+$ 517.

[7] Following the coupling reaction, the product was purified by flash column chromatography eluting with methanol (4%) and methylene chloride (96%) gave a foam. This was re-precipitated by stirring in diethyl ether (20ml) to give 4-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-2-methyl-4-oxobutan-2-ol as a white solid (0.232 g); ^{1}H NMR Spectrum: (DMSO d_6) 1.20 (s, 6H), 1.54-1.77 (m, 2H), 2.04 (m, 2H), 2.49 (s, 2H), 3.30 (m, 1H), 3.45 (m, 1H), 3.86 (m, 1H), 3.96 (s, 3H), 4.00 (m, 1H), 4.88 (s, 1H), 4.91 (1H, m), 7.28 (m, 1H), 7.35 (s, 1H), 7.47 (m, 1H), 7.54 (m, 1H), 7.83 (s, 1H), 8.40 (s, 1H), 9.63 (br s, 1H); Mass Spectrum: $(M+H)^+$ 503.

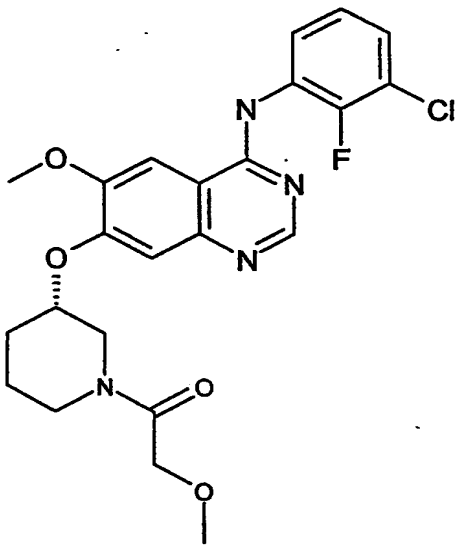
[8] Following the coupling reaction, the product was purified by flash column chromatography eluting with methylene chloride / 7N ammonia solution in methanol (98/2) gave a foam. This was re-precipitated by stirring in diethyl ether (20 ml) to give *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl]oxy}quinazolin-4-amine as a white solid (0.260 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.73 (m, 2H), 1.99 (m, 2H), 2.05 (m, 3H), 2.14 (m, 1H), 3.48 (m, 2H), 3.83 (m, 4H), 3.99 (s, 3H), 4.69 (t, J=7Hz, 1H), 4.89 (1H, m), 7.29 (m, 1H), 7.37 (s, 1H), 7.43 (m, 1H), 7.60 (m, 1H), 7.83 (s, 1H), 8.39 (s, 1H), 9.33 (br s, 1H); Mass Spectrum: $(M+H)^+$ 501.

[9] Following the coupling reaction, the product was purified by flash column chromatography eluting with methanol (4%) and methylene chloride (96%) gave a foam. This was re-precipitated by stirring in diethyl ether (20 ml) to give 3-[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-2,2-dimethyl-3-oxopropan-1-ol as a white solid (0.244g). ^{1}H NMR Spectrum : (DMSO d_6) 1.10 (s, 6H), 1.64 (m, 2H), 2.03 (m, 2H), 3.39 (m, 2H), 3.45 (m, 2H), 3.95 (s, 3H), 3.98 (m, 2H), 4.54 (t, J=6Hz, 1H), 4.91 (1H, m), 7.29 (m, 1H), 7.35 (s, 1H), 7.48 (m, 1H), 7.53 (m, 1H), 7.83 (s, 1H), 8.39 (s, 1H), 9.64 (br s, 1H); Mass Spectrum : $(M+H)^+$ 503.

[10] (3*R*,5*S*)-1-Acetyl-5-{[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]carbonyl}pyrrolidin-3-ol (0.160 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.65-1.87 (m, 3H), 1.93 (s, 3H), 2.04 (m, 3H), 3.44-3.64 (m, 4H), 3.81 (m, 2H), 3.98 (s, 3H), 4.28-4.39 (m, 1H), 4.71 (m, 1H), 4.89 (m, 2H), 7.23 (m, 1H), 7.32 (s, 1H), 7.40 (m, 1H), 7.59 (m, 1H), 7.81 (s, 1H), 8.39 (s, 1H), 9.29 (br s, 1H); Mass Spectrum: $(M+H)^+$ 558.

Example 5

***N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[(3*S*)-1-(methoxyacetyl)piperidin-3-yl]oxy}quinazolin-4-amine**



HATU (0.24 g) was added to a solution of *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*S*)-piperidin-3-yloxy]quinazolin-4-amine dihydrochloride (250 mg), diisopropylethylamine (0.37 ml) and methoxyacetic acid (0.054 g) in methylene chloride (9 ml) and the mixture was stirred at room temperature for 2.5 hours. Methylene chloride (20 ml) was added and the organic layer was washed with aqueous sodium hydroxide (2M, 30 ml) and water (30 ml). The resulting product was purified by flash column chromatography eluting with methanol (3%) and methylene chloride (97%) gave a foam. This was re-precipitated by stirring in diethyl ether (20ml) to give the title product as a white solid (0.202 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.60 (m, 1H), 1.88 (m, 2H), 2.10 (m, 1H), 3.32 (s, 3H), 3.51 (m, 2H), 3.62 (m, 1H), 3.87 (m, 1H), 3.98 (s, 3H), 4.02 (d, J=14Hz, 1H), 4.12 (d, J=14Hz, 1H), 4.66 (m, 1H), 7.26 (m, 1H), 7.33 (s, 1H), 7.43 (m, 1H), 7.62 (m, 1H), 7.83 (s, 1H), 8.40 (s, 1H), 9.34 (br s, 1H); Mass Spectrum : $(M+H)^+$ 475.

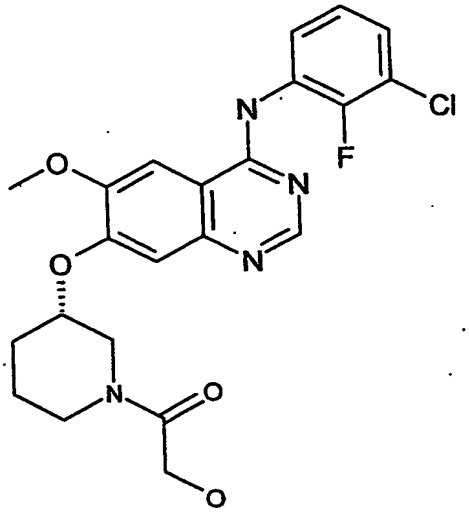
The *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*S*)-piperidin-3-yloxy]quinazolin-4-amine dihydrochloride used as starting material was prepared as follows:

Diethylazodicarboxylate (3.73 g) was added dropwise to a mixture of *tert*-butyl (3*R*)-3-hydroxypiperidine-1-carboxylate (4.29 g), 4-chloro-6-methoxyquinazolin-7-ol (CAS Registry Number: 263400-68-6) (3.00 g) and triphenylphosphine (5.61 g) in methylene chloride (75 ml). The solution was then heated to 40°C and stirred for 3 hours. After cooling the mixture was filtered and then purified by flash column chromatography eluting with isohexane/acetone/triethylamine (80/20/1) to give *tert*-butyl (3*S*)-3-[(4-chloro-6-methoxyquinazolin-7-yl)oxy]piperidine-1-carboxylate as a colourless oil (3.29 g) which was used directly; Mass Spectrum: $(M+H)^+$ 394.

4.0M HCl in dioxane (6.0 ml) was added to a stirred suspension of *tert*-butyl (3*S*)-3-[(4-chloro-6-methoxyquinazolin-7-yl)oxy]piperidine-1-carboxylate (3.21 g) and 3-chloro-2-fluoroaniline (0.98ml) in acetonitrile (50mL). The reaction mixture was heated at 80°C and left at this temperature overnight. The solvent was evaporated and the residue purified by flash column chromatography eluting with increasingly polar mixtures of methylene chloride/7N ammonia solution in methanol (97/3 to 95/5) to give *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*S*)-piperidin-3-yloxy]quinazolin-4-amine dihydrochloride as a solid (3.20 g); ^{1}H NMR Spectrum: (DMSO d_6) 1.56 (m, 2H), 1.72 (m, 1H), 2.12 (m, 1H), 2.48-2.59 (m, 2H), 2.82 (m,1H), 3.20 (m, 1H), 3.95 (s, 3H), 4.49 (m, 1H), 7.26 (s, 1H), 7.28 (m, 1H), 7.47 (m, 1H), 7.53 (m, 1H), 7.81 (s, 1H), 8.38 (s, 1H), 9.63(s, 1H); Mass Spectrum: $(M+H)^+$ 403.

Example 6

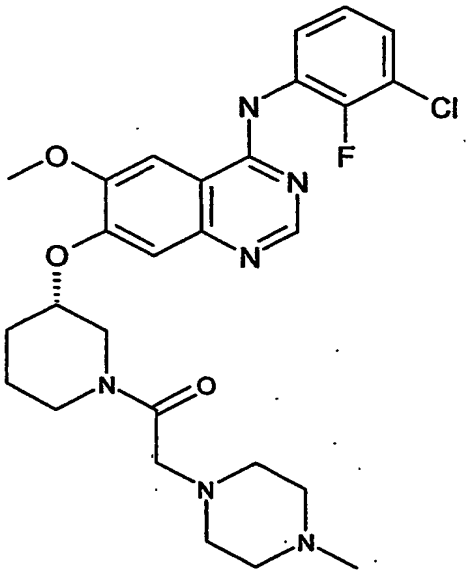
2-[(3*S*)-3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]-2-oxoethanol



Using an analogous procedure to that described in Example 5 *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*S*)-piperidin-3-yloxy]quinazolin-4-amine dihydrochloride (250mg) was coupled with glycolic acid (0.045g). The resulting product was purified by flash column chromatography eluting with methanol (3%) and methylene chloride (97%) to give a foam. This was re-precipitated by stirring in diethyl ether (20ml) to give the title product as a white solid (0.105 g); ^{1}H NMR Spectrum: (DMSO d_6 373K) 1.59 (m, 1H), 1.87 (m, 2H), 2.09 (m, 1H), 3.40-3.60 (m, 4H), 3.86 (m, 1H), 3.98 (s, 3H), 4.04-4.18 (m, 2H), 4.66 (m, 1H), 7.24 (m, 1H), 7.31 (s, 1H), 7.40 (m, 1H), 7.60 (m, 1H), 7.80 (s, 1H), 8.38 (s, 1H), 9.30 (br s, 1H); Mass Spectrum: $(M+H)^+$ 461.

Example 7

***N*-(3-Chloro-2-fluorophenyl)-6-methoxy-7-({(3*S*)-1-[(4-methylpiperazin-1-yl)acetyl]piperidin-3-yl}oxy)quinazolin-4-amine**

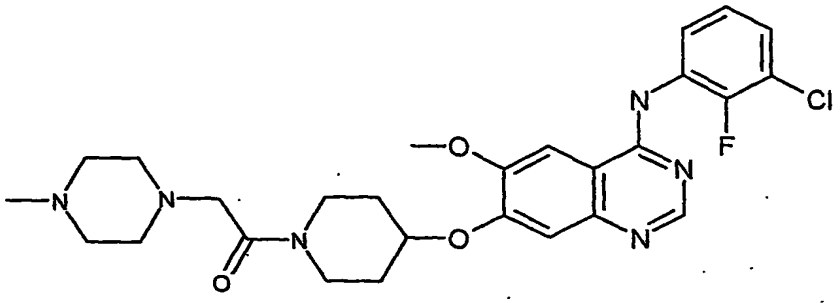


Chloroacetyl chloride (47 µl) was added to a solution of *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*S*)-piperidin-3-yloxy]quinazolin-4-amine dihydrochloride (250 mg) and diisopropylethylamine (373 µl) in methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 1 hour. 1-Methylpiperazine (228 mg) was added, and the solution stirred for 1 hour before being washed with aqueous sodium hydroxide (2M, 10 ml) and water (10 ml). The organics were then purified by flash column chromatography eluting with methylene chloride/7N ammonia solution in methanol (97/3) to give a foam. This was re-precipitated by stirring in diethyl ether (20 ml) to give the title product as a white solid (0.135g); ^{1}H NMR Spectrum: (DMSO d_6) 1.42-1.67 (m, 1H), 1.70-1.95 (m, 2H), 1.98-2.48 (m, 9H), 2.18 (s, 3H), 2.82-3.05 (m, 1H), 3.20-4.02 (m, 8H), 4.68 (m, 1H,), 7.30 (m, 1H), 7.34

(s, 1H), 7.44-7.60 (m, 2H), 7.82 (m, 1H), 8.38 (s, 1H), 9.64 (m, 1H); Mass Spectrum: $(M+H)^+$ 543.

Example 8

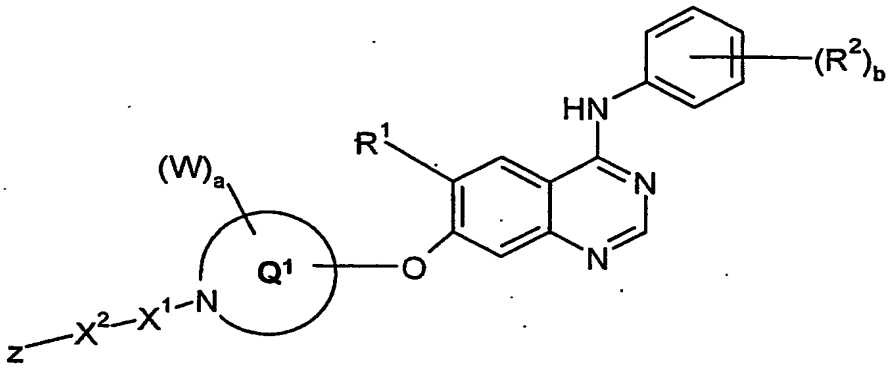
***N*-(3-Chloro-2-fluorophenyl)-6-methoxy-7-({1-[(4-methylpiperazin-1-yl)acetyl]piperidin-4-yl}oxy)quinazolin-4-amine**



Using an analogous procedure to that described in Example 7 *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride (250mg) was reacted with chloroacetyl chloride (47 μl), followed by 1-Methylpiperazine (228mg) and purification to give the title product as a white solid (0.110 g); ^{1}H NMR Spectrum: (DMSO d_6) 1.57 (m, 1H), 1.72 (m, 1H), 1.96-2.12 (m, 2H), 2.15 (s, 3H), 2.27-2.48 (m, 8H), 3.08-3.52 (m, 4H), 3.86-4.04 (m, 2H), 3.95 (s, 3H), 4.90 (m, 1H,), 7.30 (m, 1H), 7.37 (s, 1H), 7.47-7.58 (m, 2H), 7.83 (s, 1H), 8.38 (s, 1H), 9.63 (s, 1H); Mass Spectrum: $(M+H)^+$ 543.

CLAIMS

1. A quinazoline derivative of the Formula I:



I

wherein:

R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is a direct bond or is O, and Q^2 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^3)$, CO, $CH(OR^3)$, $CON(R^3)$, $N(R^3)CO$, $SO_2N(R^3)$, $N(R^3)SO_2$, CH=CH and C≡C wherein R^3 is hydrogen or (1-6C)alkyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^3-X^4-$$

wherein X^3 is a direct bond or is selected from CO and $N(R^4)CO$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:

$$-X^5-Q^4$$

wherein X^4 is a direct bond or is selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, $C(R^5)_2O$, $C(R^5)_2S$ and $C(R^5)_2N(R^5)$, wherein R^5 is hydrogen or (1-6C)alkyl, and Q^4 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears one or more (for example 1, 2 or 3) substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, mercapto, sulfamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:

$$-X^6-R^6$$

wherein X^6 is a direct bond or is selected from O, $N(R^7)$ and C(O), wherein R^7 is hydrogen or (1-6C)alkyl, and R^6 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,

(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

b is 1, 2, 3, 4 or 5;

each R^2, which may be the same or different, is selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino and a group of the formula :

$$-X^7-R^8$$

wherein X^7 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl;

Q^1 is piperidinyl;

a is 0, 1, 2, 3 or 4;

each W, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, oxo, amino, formyl, mercapto, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^8-R^{10}$$

wherein X^8 is a direct bond or is selected from O, CO, SO_2 and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and R^{10} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, N-(1-6C)alkylamino-(1-6C)alkyl or N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl;

X^1 is selected from CO and SO_2;

X^2 is a group of the formula:

$$-(CR^{12}R^{13})_p-(Q^5)_m-(CR^{14}R^{15})_q-$$

wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

each of R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, is selected from hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q^5 is selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,

and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:

$$Q^6-X^9-$$

wherein X^9 is a direct bond or is selected from O, $N(R^{16})$, SO_2 and $SO_2N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^{17})$, CO, -C=C- and -C≡C- wherein R^{17} is hydrogen or (1-6C)alkyl,

and wherein and wherein any CH_2 or CH_3 group within any Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-X^{10}-R^{18}$$

wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $N(R^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

provided that:

when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino and R^1 is hydrogen or (1-3C)alkoxy, then a is 0 and Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q^6-X^9-;

or a pharmaceutically acceptable salt thereof.